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por el

DR. LUIS RAZETTI

Organo de la Academia Nacional de Medicina
y del Congreso Venezolano de Ciencias Médicas

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de Caracas

Órgano oficial de la Academia Nacional de Medicina
y del Congreso Venezolano de Ciencias Médicas

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Manuel Velasco

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Muhammad Miftahussurur

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de Caracas

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Guest Editor
Muhammad Miftahussurur

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La GMC sigue las Recomendaciones para la realización, informe, edición y publicación de trabajos académicos en revistas médicas, del Comité Internacional de Editores de Revistas Médicas conocidas como Recomendaciones ICMJE [www.ICMJE.org, Gac Méd Caracas. 2020;128(1):77-111]. Las unidades deben presentarse de acuerdo con el Sistema Internacional de Unidades (SI) [Gac Méd Caracas. 2015;123(1):46-71].

En la GMC se dará cabida a los trabajos realizados por profesionales de la medicina o especialidades conexas, presentados en la Academia, en los Congresos de Ciencias Médicas y los que sugiera la Corporación a través del Comité Científico, y aceptación final por la Dirección-Redacción. Los manuscritos enviados a la GMC —escritos en español o en inglés—, serán revisados por el Comité Editorial y— si reunen la calidad científica y cumplen con las normas de presentación necesarias— serán sometidos a un proceso de arbitraje externo por personas con competencias similares a las de los productores del trabajo (pares) para su debida evaluación. Queda entendido que el Comité Editorial puede rechazar un manuscrito, sin necesidad de acudir al proceso de arbitraje, si se incumple con lo mencionado.

La opinión, crítica y recomendaciones de los revisores son recibidas en forma escrita y anónima y se enviarán a los autores, cuando así lo decida la Dirección-Redacción.

Todos los trabajos deberán ser enviados por Internet y en papel escrito en computadora a doble espacio, letra Times New Roman tamaño 12, por el anverso del papel, tamaño carta, con amplio margen libre en todo el contorno.

La GMC considerará contribuciones para las siguientes secciones:

Artículos de revisión
Artículos originales
Artículos especiales
Casos clínicos
Historia y filosofía de la medicina
Información epidemiológica
Bioética
Comunicaciones breves
Perlas de observación
Noticias y cartas al editor
Varios

Los trabajos enviados deberán cumplir con los requisitos que se describen a continuación.

EDITORIALES

Esta sección estará dedicada al análisis y la reflexión sobre los problemas de salud de la población, los distintos enfoques preventivos y terapéuticos, así como los avances logrados en el campo de la investigación biomédica y otros que considere la Dirección-Redacción.

ARTÍCULOS ORIGINALES

Deberán contener en la página frontal, el título conciso e informativo del trabajo; nombre(s) y apellido(s) de cada autor; grados académicos de los autores e institución en la cual se realizó el trabajo; nombre y dirección actual del autor responsable de la correspondencia; un título corto de no más de 40 caracteres (contando espacios y letras) y las palabras clave.

Los trabajos originales, revisiones sistemáticas y metanálisis deben tener un resumen estructurado, como se indica a continuación:

Debe contener un máximo de 250 palabras, y los siguientes segmentos:

- Introducción: ¿Cuál es el problema principal que motivó el estudio?
- Objetivo: ¿Cuál es el propósito del estudio?
- Métodos: ¿Cómo se realizó el estudio? (selección de la muestra, métodos analíticos y observacionales).
- Resultados: ¿Cuáles son los aspectos más importantes? (datos concretos y en lo posible su significancia estadística)
- Conclusión: ¿Cuál es la más importante que responde al objetivo?

Al final se anotarán 3 a 6 palabras clave.

Resumen en inglés

Debe corresponderse con el resumen en español. Se sugiere que este sea revisado por un traductor experimentado, a fin de garantizar la calidad del mismo.

Introducción

Incluir los antecedentes, el planteamiento del problema y el objetivo del estudio en una redacción libre y continua debidamente sustentada por la bibliografía.

Método

Señalar claramente las características de la muestra, el o los métodos empleados con las referencias pertinentes, de forma que se permita a otros investigadores, realizar estudios similares.

Resultados

Incluir los hallazgos importantes del estudio, comparándolos con las figuras estrictamente necesarias y que amplíen la información vertida en el texto.

Discusión

Relacionar los resultados con lo reportado en la literatura y con los objetivos e hipótesis planteados en el trabajo.

Conclusión

Describir lo más relevante que responda al objetivo del estudio.

Agradecimientos

En esta sección se describirán los agradecimientos a personas e instituciones así como los financiamientos.

Referencias

Se presentarán de acuerdo con las Recomendaciones ICMJE.

Indicarlas con números arábigos entre paréntesis en forma correlativa y en el orden en que aparecen por primera vez en el texto, cuadros y pie de las figuras. En las citas de revistas con múltiples autores (más de seis autores), se deberá incluir únicamente los 6 primeros autores del trabajo, seguido de et al.,

a. Artículos en revistas o publicaciones periódicas: apellido(s) del autor(es), inicial del nombre(s). Título del artículo. Abreviatura internacional de la revista: año; volumen: páginas, inicial y final. Ejemplo: Puffer R. Los diez primeros años del Centro Latinoamericano de la Clasificación de Enfermedades. Bol. Of San Pam. 1964;57:218-229.
b. Libros: apellido(s) del autor(es), inicial(es) del nombre(s). Título del libro. Edición. Lugar de publicación (ciudad): casa editora; año. Ejemplo: Plaza Izquierdo F. Doctores venezolanos de la Academia Nacional ade Medicina. Caracas: Fundación Editorial Universitaria, 1996. (No lleva "Edición" por tratarse de la primera).
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Fotografías

Las fotografías de objetos incluirán una regla para calibrar las medidas de referencia.

En las microfotografías deberá aparecer la ampliación microscópica o una barra de micras de referencia.

Congreso de Ciencias Médicas

Se publicarán únicamente trabajos originales de presentaciones en Congresos de Ciencias Médicas. Serán enviados a la Gaceta por los coordinadores, quienes se responsabilizarán de la calidad, presentación de los manuscritos, secuencia y estructura, incluyendo un resumen general en español y en inglés, en formato libre y que no excedan de 250 palabras. Cada contribución no excederá de 10 cuartillas y deberá apegarse a lo señalado en estas instrucciones a los autores.

Artículos de revisión

Versarán sobre un tema de actualidad y de relevancia médica. El autor principal o el correspondiente deberá ser una autoridad en el área o tema que se revisa y anexará una lista bibliográfica de sus contribuciones que avale su experiencia en el tema.

Las secciones y subtítulos serán de acuerdo con el criterio del autor. Incluir un resumen general en español y en inglés que no exceda de 150 palabras. La extensión máxima del trabajo será de 20 cuartillas. Las ilustraciones deberán ser las estrictamente necesarias, no siendo más de seis, la bibliografía suficiente y adecuada y en la forma antes descrita.

Artículos especiales

Son aquellas contribuciones que por su importancia el Comité Redactor considere su inclusión en esta categoría.

Casos clínicos

Deberán constar de resumen en español e inglés (máximo 100 palabras) en formato libre. Constará de introducción, presentación del caso, discusión, ilustraciones y referencias, con una extensión máxima de 10 cuartillas y apegadas a las instrucciones a los autores.

Historia y filosofía de la medicina

En esta sección se incluirán los artículos relacionados con aspectos históricos, filosóficos, bases conceptuales y éticas de la medicina. Aunque su estructura se dejará a criterio del autor, deberá incluir resúmenes en español e inglés (máximo 100 palabras) en formato libre, referencias bibliográficas citadas en el texto y en listadas al final del manuscrito, siguiendo los lineamientos citados para los manuscritos de GMC.

Actualidades terapéuticas

Se informará sobre los avances y descubrimientos terapéuticos más recientes aparecidos en la literatura nacional e internacional y su aplicación en nuestro ámbito médico. La extensión máxima será de cuatro cuartillas y con un máximo de cinco referencias bibliográficas. Deberá incluir resúmenes en español en inglés, en formato libre (máximo 100 palabras).

Información epidemiológica

Será una sección de información periódica sobre los registros epidemiológicos nacionales e internacionales, destacando su importancia, su comparación con estudios previos y sus tendencias proyectivas. La extensión máxima será de cuatro cuartillas y deberá incluir resúmenes en español en inglés (máximo 100 palabras), en formato libre.

Comunicaciones breves

Serán considerados en esta sección, los informes preliminares de estudios médicos y tendrán la estructura formal de un resumen como se describió previamente (máximo 150 palabras). Se deberán incluir 10 citas bibliográficas como máximo.

Bioética

Se plantearán los aspectos éticos del ejercicio profesional y aquellos relacionados con los avances de la investigación biomédica y sus aplicaciones preventivas y terapéuticas. Su extensión máxima será de cuatro cuartillas y cuatro referencias bibliográficas, deberá incluir resúmenes en español e ingles (máximo 100 palabras) en formato libre.

El médico y la ley

Esta sección estará dedicada a contribuciones tendientes a informar al médico acerca de las disposiciones legales, riesgos y omisiones de la práctica profesional que puedan conducir a enfrentar problemas legales. Su máxima extensión será de cuatro cuartillas y no más de cinco referencias bibliográficas. Deberá incluir resúmenes en español e inglés (máximo 100 palabras).

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No se aceptarán artículos para su revisión si no están preparados de acuerdo a las Instrucciones para los Autores. Se enviará un recibo electrónico al autor y en tiempo oportuno se le comunicará el dictamen del Editor.

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Multidisciplinary Research in Medicine Science during COVID-19 Pandemic

Muhammad Miftahussurur

Guest Editor

It is a great honor to be Guest Editor of this special number of Gaceta Médica de Caracas. We especially appreciate the invitation of the Board of Directors of the Medicine Academy and the Editor-in-Chief, Dr. Manuel Velasco, to prepare this supplement, as well as the great support, received from the Senior Editor, Dr. Anita Stern Israel.

Since 2020 we have experienced the COVID-19 pandemic which has had an impact on many aspects, not only affecting lives and health, but also livelihoods, economy, and behaviors. The spread of COVID-19 in Indonesia is now increasingly widespread, with the number of cases exposed to COVID -19 increasing day by day. We must be careful in dealing with the spread of this virus since there is a continuous increase in the number of people infected with COVID-19. COVID-19 also reminds us that prevention is always better than cure. This is an old expression used for decades, but never properly implemented by our society today.

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COVID-19 has an impact on the whole health system. Health care providers are forced to take care of the healthcare provision quality and overcoming limitations arising from this challenging time. All health care providers need to suit their skills and knowledge to work in this progressing healthcare situation in various facilities.

COVID-19 is a highly contagious disease and affects different people in different ways. Most infected people will develop various degrees of severity from mild to critical conditions. A study by *Witarto et al*. presented the evaluation of serum HDL-c and LDL-c levels in predicting the COVID-19 severity. They conducted a systematic method and demonstrated that serum HDL-c levels may serve as a better predictor of COVID-19 severity than serum LDL-c levels. Another study by *Prajitno et al*. carried out the educational intervention for the use of face masks in the community and evaluated the changes after the intervention. They revealed the improvement both in knowledge and behavior. Moreover, *Alfaray et al*. reported the role of the youth generation to increase the scope target of health promotion and health prevention of COVID-19 and Hepatitis B. They described their motivation to join the ambassador program, their commitment, and their knowledge regarding Surabaya, COVID-19, and Hepatitis B. They also analyzed the correlation between the respondents'

age and their commitment as well as their commitments and the degree of their knowledge.

Besides studies regarding COVID-19, this supplement also presents several clinical studies not limited to internal medicine, but also physiology, neurology, and others. A study by *Hamida et al*. assessed the HbA1c levels and the occurrence of diabetic neuropathy and revealed that uncontrolled HbA1c levels had a higher risk of diabetic neuropathy complications than the controlled group. In addition, *Wironegoro et al*. compared the IgE level and Thyroid-Stimulating Hormone Receptor Antibody (TRAb) level among Graves' disease based on atopy status. They found that IgE and TRAb levels among respondents with a history of atopy were significantly higher than those without a history of atopy. Another study by *Machin et al*. investigated the malondialdehyde (MDA) levels with clinical outcomes assessed using the modified Rankin Scale (mRS) in patients with acute intracerebral hemorrhagic stroke. The study demonstrated that patients with high MDA levels had a 1.9 times higher risk of experiencing poor clinical outcomes of mRS compared to subjects who had low MDA levels.

All the manuscripts in this supplement are written in English and involve multiple areas of medicine, includes 31 articles, 29 are original articles, one is a systematic review, and one is a narrative review. We hope the understanding and dissemination of these articles will strengthen the innovations that have come out in recent years correlated to, not only internal medicine but also in the whole medical field.

Investigación multidisciplinaria en ciencia de la medicina durante la pandemia de COVID-19

Muhammad Miftahussurur

Editor Invitado

Es un gran honor ser Editor Invitado de este número especial de Gaceta Médica de Caracas. Agradecemos especialmente la invitación de la Junta Directiva de la Academia de Medicina y del Editor en Jefe, Dr. Manuel Velasco, para preparar este suplemento, así como el gran apoyo recibido de la Editora Senior, Dra. Anita Stern Israel.

Desde 2020 hemos vivido la pandemia del COVID-19, la cual ha impactado en muchos aspectos, no solo afectando la vida y la salud, sino también los medios de vida, la economía y el comportamiento. La propagación del COVID-19 en Indonesia está cada vez más extendida, y el número de casos expuestos al COVID-19 aumenta día a día. Debemos tener cuidado al lidiar con la propagación de este virus ya que siempre hay un aumento en el número de personas infectadas con COVID-19.

COVID-19 también nos recuerda que siempre es mejor prevenir que curar. Esta es una expresión antigua utilizada durante décadas, pero que en la actualidad nuestra sociedad no ha implementado correctamente. COVID-19 tiene un impacto en todo el sistema de salud. Los proveedores de atención médica se ven obligados a cuidar la calidad de la prestación de atención médica y superar las limitaciones que surgen de este momento desafiante. Todos los proveedores de atención médica deben adaptarse a sus habilidades y conocimientos para trabajar en esta situación de atención médica en progreso en varias instalaciones.

COVID-19 es una enfermedad altamente contagiosa y afecta a diferentes personas de diferentes maneras. La mayoría de las personas infectadas desarrollarán diversos grados de gravedad, desde afecciones leves a críticas. Un estudio de *Witarto y col*. presentó la evaluación de los niveles séricos de HDL-c y LDL-c para predecir la gravedad de COVID-19. Llevaron a cabo un método sistemático y demostraron que los niveles séricos de HDL-c pueden servir como un mejor predictor de la gravedad de la enfermedad de COVID-19 que los niveles séricos de LDL-c. Otro estudio de *Prajitno y col*. realizó la intervención educativa para el uso de mascarillas en la comunidad y evaluó los cambios posteriores a la intervención. Revelaron la mejora tanto en el conocimiento como en el comportamiento. Por otra parte, *Alfaray y col*. reportaron el papel de la generación joven para incrementar el alcance de la meta de promoción

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y prevención de la salud de COVID-19 y hepatitis B. Ellos describieron su motivación para unirse al programa de embajadores, su compromiso y sus conocimientos sobre Surabaya, COVID-19 y hepatitis B. También analizaron la correlación entre la edad de los encuestados y su compromiso, así como sus compromisos y el grado de conocimiento.

Además del estudio sobre COVID-19, este suplemento también presenta varios estudios clínicos que no se limitan a la medicina interna, sino también a la fisiología, neurología y otros. En un estudio de *Hamida y col*. Se evaluaron los niveles de HbA1c y la aparición de neuropatía diabética y revelaron que los niveles de HbA1c no controlados tenían un mayor riesgo de complicaciones de neuropatía diabética que el grupo controlado. Además, *Wironegoro y col*. compararon el nivel de IgE y el nivel de anticuerpos receptores de hormonas estimulantes de la tiroides (TRAb) entre la enfermedad de Graves en función del estado de atopia. Descubrieron que el nivel de IgE y el nivel de TRAb entre los encuestados con antecedentes de atopia eran significativamente más altos que los que no tenían antecedentes de atopia. Además, otro estudio de *Machin y col*. investigó los niveles de malondialdehído (MDA) con resultados clínicos evaluados mediante la escala de Rankin modificada (mRS) en pacientes con accidente cerebrovascular hemorrágico intracerebral agudo. El estudio demostró que los niveles altos de MDA tenían un riesgo 1,9 veces mayor de experimentar resultados clínicos deficientes de la mRS en comparación con los sujetos que tenían niveles bajos de MDA.

Todos los manuscritos de este suplemento están escritos en inglés y consisten en múltiples áreas de la medicina, consta de 31 artículos, de los cuales 29 son artículos originales, uno es una revisión sistemática y otro es una revisión narrativa. Esperamos que la comprensión y la difusión de estos artículos fortalezcan las innovaciones que han surgido en los últimos años relacionadas no solo con la medicina interna sino también en todo el campo de la medicina.

ARTÍCULO ORIGINAL

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Serum HDL-c and LDL-c levels as the predictors of COVID-19 severity

Niveles séricos de HDL-c y LDL-c como predictores de la severidad por COVID-19

Andro P. Witarto[1*•], Achmad J. E. Putra[2*], Shidi L. Pramudito[3*]

SUMMARY

Background: Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) and comes with various degrees of severity from mild to critical conditions. This study aims to evaluate and clarify the roles of serum HDL-c and LDL-c levels in predicting the COVID-19 severity.
Methods: A systematic search was conducted in four electronic databases, including Scopus, PubMed, SAGE, and CINAHL Plus database in EBSCOhost. The identified articles were screened based on the specified eligibility criteria. The Newcastle-Ottawa Scale (NOS) tool was further used to assess the risk of bias of each included study.
Results: Seven observational studies were included in the qualitative synthesis of this systematic review. In 6 studies (85.71 %), serum HDL-c levels were significantly lower in the severe COVID-19 compared to the non-severe group ($p< 0.05$). One of those 6 studies showed that significantly lower serum HDL-c levels were also found in critical cases of COVID-19 as compared to the severe cases. Serum HDL-c levels were also negatively correlated to the COVID-19 severity ($p= 0.0001$; $r= -0.362$) in one study and had a protective effect towards COVID-19 ($p= 0.001$; age-adjusted OR [95 %CI] = 0.023 [0.002-0.227]) in one other study. However, 5 studies (71.42 %) showed that serum LDL-c levels were not significantly different between severe and non-severe COVID-19 ($p > 0.05$).
Conclusion: Serum HDL-c levels may serve as a better predictor of the disease severity of COVID-19 than serum LDL-c levels.

Keywords: *Cholesterol, COVID-19, HDL, LDL, SARS-CoV-2, severe, systematic review.*

RESUMEN

Antecedentes: *La enfermedad por coronavirus 2019 (COVID-19) es una enfermedad altamente contagiosa causada por el coronavirus del síndrome de dificultad respiratoria aguda grave 2 (SARS-CoV-2) y se presenta con varios grados de gravedad, desde condiciones leves a críticas. Este estudio tiene como objetivo evaluar y aclarar las funciones de los niveles séricos de HDL-c y LDL-c en la predicción de la gravedad de COVID-19.*
Métodos: *Se realizó una búsqueda sistemática en cuatro bases de datos electrónicas, incluyendo la base de datos Scopus, PubMed, SAGE y CINAHL Plus en EBSCOhost. Los artículos identificados se examinaron según los criterios de elegibilidad especificados. La herramienta Newcastle-Ottawa Scale (NOS) se utilizó además para evaluar el riesgo de sesgo de cada estudio incluido.*

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Resultados: *Se incluyeron siete estudios observacionales en la síntesis cualitativa de esta revisión sistemática. En 6 estudios (85,71 %), los niveles séricos de HDL-c fueron significativamente más bajos en el grupo de COVID-19 grave en comparación con el grupo no grave (p< 0,05). Uno de esos 6 estudios mostró que también se encontraron niveles de HDL-c sérico significativamente más bajos en casos críticos de COVID-19 en comparación con los casos graves. Los niveles séricos de HDL-c también se correlacionaron negativamente con la gravedad de COVID-19 (p= 0,0001; r= -0,362) en un estudio y tuvieron un efecto protector frente a COVID-19 (p= 0,001; OR ajustado por edad [IC del 95 %] = 0,023 [0,002-0,227]) en otro estudio. Sin embargo, 5 estudios (71,42 %) mostraron que los niveles séricos de LDL-c no eran significativamente diferentes entre COVID-19 grave y no grave (p> 0,05).*
Conclusión: *Los niveles séricos de HDL-c pueden servir como un mejor predictor de la gravedad de la enfermedad de COVID-19 que los niveles séricos de LDL-c.*

Palabras clave: *Colesterol, COVID-19, HDL, LDL, SARS-CoV-2, grave, revisión sistemática.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by a new recombinant virus, the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), and transmitted person-to-person through the droplet from coughs, talks, or sneezes, with a variety of symptoms, including fever, cough, shortness of breath, anosmia, ageusia, chills, headache, muscle soreness, and sore throat. These could persist for 2-14 days (1,2). In the COVID-19 weekly epidemiological update by World Health Organization (WHO), as of 1 November 2020, the number of COVID-19 cases reaches over 46 million cases with 1.2 million deaths globally (3). The general cases were classified into three groups: the confirmed case, the probable case, and the suspected case (4). Moreover, the clinical outcomes were further divided into five groups: asymptomatic cases with a positive result on SARS-CoV-2 nucleic acid test and no sign or symptoms or any radiological findings; mild cases with mild symptoms in the upper respiratory or digestive system, including fever, myalgia, fatigue, diarrhea, or nausea; moderate cases with a lung lesion on chest CT; severe cases with a lung lesion on chest CT and hypoxemia <92 %; and critical cases with the presence of acute respiratory distress syndrome (ARDS) and several complications, including shock, myocardial injury, acute kidney injury, or encephalopathy (5,6).

Although COVID-19 came with various degrees of severity, some mild patients could rapidly progress to severe or even critical states of COVID-19. Early identification of the risk factors of the critical cases could increase our awareness to further facilitate early supportive care and reduce COVID-19 mortality (7). One of them was lipid profiles, as lipids were important in supporting the viral entry (8,9). SARS-CoV-2 was believed to alter the lipid metabolism in the host cells. A decline in serum high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) levels was observed in the laboratory results of COVID-19 patients (10). It was thought to be caused by the interaction of HDL-c with the spike protein of SARS-CoV-2 and the increased oxidation of LDL-c to oxLDL. Both together could induce further inflammatory processes and increase the severity of COVID-19 (7,11). However, to date, there is no specific study defining and summarizing the actual benefit of HDL-c and LDL-c in predicting the COVID-19 severity due to the lack of evidence. In this systematic review, we will evaluate and clarify the role of HDL-c and LDL-c in determining the degree of COVID-19 severity.

METHODS

Search Strategy

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement from four electronic medical databases, including Scopus, PubMed, SAGE, and CINAHL Plus database in EBSCOhost. Data search was conducted independently by all authors with inception to 17 October 2020. Keywords used were the combination of Medical Subject Headings (MeSH) terms and other additional terms, and listed as follows: ((“COVID-19”) OR (“COVID19”) OR (“Sars-CoV-2 infection”) OR (“2019-nCoV infection”)

OR ("coronavirus disease 2019")) AND (("HDL") OR ("LDL") OR ("cholesterol") OR ("lipids") OR ("dyslipidemia")) AND (("severe") OR ("severity") OR ("intensive care units")). The search was limited to human participants and restricted to the English language.

Eligibility Criteria

Studies were screened according to the following inclusion criteria: 1) observational study, including case-control study, cross-sectional study, and cohort study; 2) study population covers adult patients (>18 years old) with a confirmed diagnosis of COVID-19 and is classified into some severity groups depending on each study; and 3) the measured outcomes were comparing serum HDL-c and LDL-c levels among the study groups. Whilst, the exclusion criteria were as follows: 1) irrelevant titles and abstracts; 2) irretrievable full-text articles; 3) wrong PICO components; 4) incompatible language; and 5) inappropriate study method.

Data Synthesis and Quality Assessment

Three investigators (AP, SL, and AJ) screened the literature and determined the studies' eligibility independently. Any disagreements were resolved in a consensus involving all authors. The extracted data were author and year of publication, the diagnostic basis of COVID-19 and its severity classification, study location, study design, study population, sample size, age of patients, serum HDL-c levels, serum LDL-c levels, and study outcomes as expressed p-value in each study. Afterward, the quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) tool to minimize the risk of bias of each study. NOS interpretation in the case-control study was classified into a good-quality study or low risk of bias (score 7-9), moderate-quality study or moderate risk of bias (score 4-6), and poor-quality studies or high risk of bias (score 0-3), while in the cross-sectional study was classified into a very good study or very low risk of bias (score 9-10), good study or low risk of bias (score 7-8), satisfactory study or moderate risk of bias (score 5-6), and unsatisfactory study or high risk of bias (score 0-4). The quality assessment was conducted by three reviewers (AP, SL, and AJ) collaboratively through a group discussion, and the final decision was taken based on all authors' agreement. Moreover, a p-value < 0.05 in each study outcome was considered statistically significant.

RESULTS

Overview of Literature Search

The initial search of this study yielded a total of 420 studies. Of those, we screened 353 titles and abstracts after duplicates removal. Forty-seven studies were further assessed based on the eligibility criteria. Finally, 7 studies were included and analyzed for qualitative synthesis. The process of study selection is provided in Figure 1.

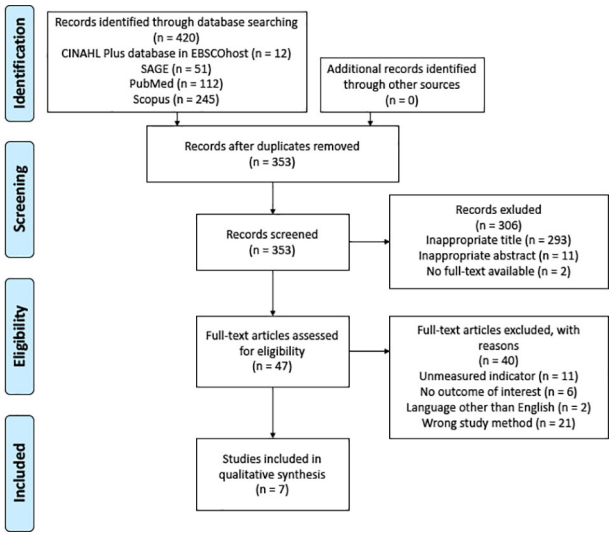

Figure 1. Study Selection Process in PRISMA flowchart.

Characteristics, Results, and Eligibility of the Selected Studies

In this systematic review, three studies were case-control studies (10,12,13) and four studies were cross-sectional studies (7,14–16). All of the eligible studies were published in 2020. Each study's diagnostic basis of COVID-19 and its severity classification was provided in Table 1.

Table 1

Diagnostic basis and severity classification of COVID-19 of the included studies

Author & Year	Diagnostic Basis of COVID-19*	Severity Classification Definition of COVID-19*
Zhang et al. (2020)	Interim guidance for novel coronavirus pneumonia (trial implementation of revised 5th edition) by Chinese National Health Committee	Participants with the diagnosis of COVID-19 were categorized into non-severe and severe groups with the following definitions of severe COVID-19: • Severe COVID-19 was considered if patients had following criteria: (a) respiratory distress with respiratory rate ≥30 breaths/min; (b) resting oxygen saturation ≤93 % on pulse oximeter; and (c) PaO2/FiO2 ≤300 mmHg.
Shu et al. (2020)	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)	Participants with the diagnosis of COVID-19 were categorized into mild-moderate and severe-critical groups based on the handbook of COVID-19 prevention and treatment 2020 by Zhejiang University School of Medicine.
D. Wang et al. (2020)	Notice on the novel coronavirus infection diagnosis and treatment plan (trial version 7) by the National Health Commission of the People's Republic of China	Participants with the diagnosis of COVID-19 were categorized into mild-moderate and severe-critical groups with the following definitions: • Mild COVID-19 was considered if patients had minor symptoms and no signs of pneumonia on imaging. • Moderate COVID-19 was considered if patients had fever, respiratory tract symptoms, and positive signs of pneumonia on imaging. • Severe COVID-19 was considered if patients had the following criteria: (a) respiratory distress with respiratory rate ≥30 breaths/min; (b) resting mean oxygen saturation ≤93 %; (c) PaO_2/FiO_2 ≤300 mmHg; (d) pulmonary imaging showed a progression of the lesion >50 % within 28-48h. • Critical COVID-19 was considered if patients had the following criteria: (a) respiratory failure requiring mechanical ventilation; (b) shock; (c) ICU admission due to multiple organ failure.
Hu et al. (2020)	Diagnosis and treatment protocols of the novel coronavirus pneumonia (trial version 7) by National Health Commission of the People's Republic of China	Participants with the diagnosis of COVID-19 were categorized into common and severe groups based on the same guideline.
Wei et al. (2020)	Guidelines of Chinese Thoracic Society and Chinese Medicine Association	Participants with the diagnosis of COVID-19 were categorized into mild, severe, and critical groups with the following definitions: • Mild COVID-19 was considered if patients had fever, cough, fatigue, headache, diarrhea, and with or without mild pneumonia. • Severe COVID-19 was considered if patients had dyspnea, acute respiratory distress, decrease in blood oxygen saturation, lung infiltrates, multiple peripheral ground-glass opacities (GGO) on both lungs. • Critical COVID-19 was considered if patients had respiratory or multiple organ failure and septic shock.

Continue on page S281…

…continuation of Table 1.

Author & Year	Diagnostic Basis of COVID-19*	Severity Classification Definition of COVID-19*
Xie et al. (2020)	Diagnosis and treatment protocols for COVID-19 (trial version 7) by National Health Commission of the People's Republic of China	Participants with the diagnosis of COVID-19 were categorized into non-severe (mild-moderate) and severe (severe-critical) groups with the following definitions: • Mild COVID-19 was considered if patients had mild symptoms and no imaging abnormalities. • Moderate COVID-19 was considered if patients had fever, coughing, and signs of pneumonia on imaging. • Severe COVID-19 was considered if patients had respiratory rate ≥30 breaths/min, or resting fingertip oxygen saturation ≤93 %, or PaO_2/FiO_2 ≤300 mmHg. • Critical COVID-19 was considered if patients had respiratory failure requiring mechanical ventilation, or symptoms of shock, or multiple organ dysfunction requiring intensive care.
G. Wang et al. (2020)	Diagnosis and treatment of new coronavirus pneumonia (trial version 6) by the National Health Commission & National Administration of Traditional Chinese Medicine (TCM)	Participants with the diagnosis of COVID-19 were categorized into non-severe and severe groups with the following definitions of severe COVID-19: • Severe COVID-19 was considered if patients had the following criteria: 1) oxygen saturation ≤93 %; 2) PaO_2/FiO_2 ≤300 mmHg; 3) respiratory rate ≥30 breaths/min; 4) receiving mechanical ventilation; 5) pulmonary lesions progressed >50 % in chest CT scan within 28-48h; 6) shock; and 7) ICU admission.

* Provided statements were collected directly from each study without any re-citations in this study
Note. COVID-19 = Coronavirus Disease 2019; CT = Computerized Tomography; FiO_2 = Fraction of Inspired Oxygen; PaO_2 = Partial Pressure of Oxygen.

A total of 2 781 participants were included from 7 studies. Of those, 1 511 participants were diagnosed with COVID-19 in all studies, except a study by Zhang et al. (2020) which included COVID-19 patients with type 2 diabetes mellitus, and 1 270 healthy controls in 3 case-control studies. Neither median nor mean of the patients' age could be summarized due to the difference in data presentation, six studies were using median (IQR) and one study by Shu et al. (2020) was using mean ± SD. One study by Wang et al. (2020) did not present the sample size of each gender and the patients' age in each group of severity.

The qualitative analysis of serum HDL-c and LDL-c levels in the participants are summarized in Table 2 and Table 3, respectively. The key finding of serum HDL-c levels in COVID-19 was 6 of 7 studies (85.71 %) – Zhang et al. (2020), D. Wang et al. (2020), Hu et al. (2020), Wei et al. (2020), Xie et al. (2020), and G. Wang et al. (2020) – generally showed significantly lower serum HDL-c levels in severe COVID-19 patients as compared to non-severe. One of them, a study by Wei et al. (2020), even showed that serum HDL-c levels in critical COVID-19 patients were significantly lower than severe patients. In addition, 2 of 7 studies by D. Wang et al. (2020) and Hu et al. (2020) also stated that serum HDL-c levels were negatively correlated to the COVID-19 severity (p= 0.000; r= -0.362) and had a protective effect towards COVID-19 (p= 0.001; age-adjusted OR [95 %CI] = 0.023 [0.002-0.227]), respectively. Whilst the key finding of serum LDL-c levels was 5 studies (71.42 %) – Zhang et al. (2020), D. Wang et al. (2020), Wei et al. (2020), Xie et al. (2020), and G. Wang et al. (2020) – generally showed

Table 2

Characteristics and Results of HDL-c Findings of the Included Studies

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of patients	Serum HDL-c Levels**	Summary of HDL-c Findings
Zhang et al. (2020)	Zhongnan Hospital of Wuhan University in Wuhan, China	Cross-sectional study	All COVID-19 patients with type 2 diabetes mellitus	All Severity	74 (36/38)	62 (56, 72)	1.03 (0.86, 1.25) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to non-severe patients (p = 0.021)
				Non-severe	47 (18/29)	61 (54, 67)	1.08 (0.96, 1.28) mmol/L	
				Severe	27 (18/9)	72 (58, 81)	0.92 (0.74, 1.20) mmol/L	
Shu et al. (2020)	Hubei Provincial Hospital of Traditional Chinese Medicine in Wuhan, China	Cross-sectional study	All confirmed and clinically diagnosis COVID-19 patients	All Severity	293 (135/158)	57.1 ± 15.6	1.1 (0.9, 1.2) mmol/L	No significant difference in HDL-c levels between severe-critical and mild-moderate COVID-19 patients (p= 0.0538)
				Mild-Moderate	207 (79/128)	54.0 ± 15.0	1.1 (0.9, 1.2) mmol/L	
				Severe-Critical	86 (56/30)	64.6 ± 14.5	1.0 (0.9, 1.2) mmol/L	
D. Wang et al. (2020)	Hubei NO.3 People's Hospital of Jianghan University in Wuhan, China	Cross-sectional study	All confirmed COVID-19 patients	All Severity	143 (73/70)	58 (39, 67)	0.9 (0.8, 1.2) mmol/L	Significantly lower HDL-c levels in severe-critical COVID-19 patients compared to mild-moderate patients (p= 0.000)
				Mild-Moderate	72 (29/43)	44 (32, 60)	1.1 (0.9, 1.3) mmol/L	
				Severe-Critical	71 (44/27)	65 (53, 69)	0.9 (0.7, 1.0) mmol/L	
Hu et al. (2020)	Wenzhou Central Hospital in Wenzhou, China	Case-control study	All PCR-confirmed COVID-19 patients and age-matched healthy subjects	Control	80 (42/38)	44.0 (36.0, 57.8)	1.27 (1.21, 1.41) mmol/L	Significantly lower HDL-c levels in all COVID-19 patients compared to controls (p< 0.001)
				All Severity	114 (60/54)	48.5 (40.8, 57.0)	1.08 (0.93, 1.08) mmol/L	

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…continuation of Table 2.

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of patients	Serum HDL-c Levels**	Summary of HDL-c Findings
				Common	87 (42/45)	46.0 (36.0, 54.0)	1.21 (1.02, 1.48) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to common patients (p< 0.001)
				Severe	27 (18/9)	62.0 (53.0, 71.0)	1.01 (0.88, 1.20) mmol/L	
Wei et al. (2020)	Cancer Center, Union Hospital of Tongji Medical College in Wuhan, China	Case-control study	All PCR-confirmed COVID-19 patients and gender- and age-matched normal healthy subjects	Control	50 (27/23)	62 (53, 69)	52 (40, 65) mg/dL	Significantly lower HDL-c levels in all COVID-19 patients compared to controls (p< 0.05)
				All Severity	597 (305/292)	66 (59, 72)	49 (41, 58) mg/dL	
				Mild	394 (189/215)	64 (53, 69)	50 (42, 59) mg/dL	Significantly lower HDL-c levels in critical COVID-19 patients compared to mild and severe patients (p< 0.05)
				Severe	171 (100/71)	69 (64, 77)	50 (41, 59) mg/dL	
				Critical	32 (16/16)	69 (61, 83)	36 (29, 43) mg/dL	Significantly lower HDL-c levels in critical COVID-19 patients compared to severe patients (p< 0.001)
Xie et al. (2020)	Department of Infectious Disease at the Cancer Center, Union Hospital of Tongji Medical College,	Cross-sectional study	All PCR-confirmed COVID-19 patients	All Severity	62 (27/35)	66.0 (53.3, 73.0)	1.2 (1.0, 2.5) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to non-severe patients (p= 0.042)
				Non-Severe				
				With CVD	16 (4/12)	66.0 (56.3, 73.0)	1.4 (1.2, 1.6) mmol/L	

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…continuation of Table 2.

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of patients	Serum HDL-c Levels**	Summary of HDL-c Findings
	Huazhong Science and Technology in Wuhan, China			Without CVD Severe	22 (10/12)	58.0 (42.8, 66.3)	1.3 (1.0, 1.5) mmol/L	Significantly lower HDL-c levels in non-severe COVID-19 patients without CVD compared to non-severe patients with CVD (p= 0.044)
				With CVD	17 (8/9)	73.0 (64.5, 83.0)	1.1 (0.9, 1.3) mmol/L	
				Without CVD	7 (5/2)	69.0 (51.0, 75.0)	1.1 (0.7, 1.7) mmol/L	No significant difference in HDL-c levels between severe COVID-19 patients with and without CVD (p= 0.726)
G. Wang et al. (2020)	Public Health Treatment Center of Changsha, China	Case-control study	All PCR-confirmed COVID-19 patients and gender- and age-matched control patients	Control	1140 (575/565)	45.5 (36.0, 60.8)	1.37 (1.22, 1.51) mmol/L	Significantly lower HDL-c levels in all COVID-19 patients compared to control (p< 0.001)
				All Severity	228 (115/113)	45.5 (36.0, 60.8)	0.78 (0.66, 0.97) mmol/L	
				Non-Severe	184	N/A	0.79 (0.69, 0.97) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to non-severe patients (p= 0.032)
				Severe	44	N/A	0.69 (0.59, 0.95) mmol/L	

* Sample size are presented in total patients (male/female)
† Age of patients are presented as years in median (interquartile range [IQR]) or mean ± SD
** Serum HDL-c levels are presented in median (interquartile range [IQR])
Note. COVID-19 = Coronavirus Disease 2019; CVD = Cardiovascular Disease; HDL-c = High-Density Lipoprotein Cholesterol; N/A = Not Available; PCR = Polymerase Chain Reaction.

Table 3

Characteristics and Results of LDL-c Findings of the Included Studies

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
Zhang et al. (2020)	Zhongnan Hospital of Wuhan University in Wuhan, China	Cross-sectional study	All COVID-19 patients with type 2 diabetes mellitus	All Severity	74 (36/38)	62 (56, 72)	2.60 (1.97, 3.25) mmol/L	No significant difference in LDL-c levels between severe and non-severe COVID-19 patients (p= 0.055)
				Non-severe	47 (18/29)	61 (54, 67)	2.76 (2.16, 3.31) mmol/L	
				Severe	27 (18/9)	72 (58, 81)	2.10 (1.63, 3.13) mmol/L	
Shu et al. (2020)	Hubei Provincial Hospital of Traditional Chinese Medicine in Wuhan, China	Cross-sectional study	All confirmed and clinically diagnosis COVID-19 patients	All Severity	293 (135/158)	57.1 ± 15.6	2.2 (1.8, 2.6) mmol/mL	Significantly lower LDL-c levels in severe-critical COVID-19 patients compared to mild-moderate patients (p= 0.0147)
				Mild-Moderate	207 (79/128)	54.0 ± 15.0	2.3 (1.9, 2.8) mmol/L	
				Severe-Critical	86 (56/30)	64.6 ± 14.5	2.0 (1.7, 2.5) mmol/L	
D. Wang et al. (2020)	Hubei NO.3 People's Hospital of Jianghan University in Wuhan, China	Cross-sectional study	All confirmed COVID-19 patients	All Severity	143 (73/70)	58 (39, 67)	2.6 (2.2, 3.0) mmol/L	No significant difference in LDL-c levels between severe-critical and mild-moderate COVID-19 patients (p= 0.615)
				Mild-Moderate	72 (29/43)	44 (32, 60)	2.6 (2.1, 3.0) mmol/L	
				Severe-Critical	71 (44/27)	65 (53, 69)	2.7 (2.2, 3.0) mmol/L	
Hu et al. (2020)	Wenzhou Central Hospital in Wenzhou,	Case-control study	All PCR-confirmed COVID-19 patients	Control	80 (42/38)	44.0 (36.0, 57.8)	3.06 (2.77, 3.06) mmol/L	Significantly lower LDL-c levels in all COVID-19
					114	48.5	2.19 (0.94,	

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…continuation of Table 3.

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
	China			All Severity	(60/54)	(40.8, 57.0)	2.73) mmol/L	patients compared to controls (p< 0.001)
				Common	87 (42/45)	46.0 (36.0, 54.0)	1.81 (1.52, 2.32) mmol/L	No significant difference in LDL-c levels between severe and common COVID-19 patients (NS)
				Severe	27 (18/9)	62.0 (53.0, 71.0)	1.88 (1.47, 2.28) mmol/L	
Wei et al. (2020)	Cancer Center, Union Hospital of Tongji Medical College in Wuhan, China	Case-control study	All PCR-confirmed COVID-19 patients	Control	50 (27/23)	62 (53, 69)	110 (96, 147) mg/dL	Significantly lower LDL-c levels in all COVID-19 patients compared to control (p< 0.001)
				All Severity	597 (305/292)	66 (59, 72)	88 (74, 102) mg/dL	
				Mild	394 (189/215)	64 (53, 69)	91 (76, 104) mg/dL	Significant decrease of LDL-c levels in COVID 19 patients across all three categories (p< 0.02)
				Severe	171 (100/71)	69 (64, 77)	86 (69, 102) mg/dL	Significantly lower LDL-c levels in mild COVID-19 patients compared to control (p< 0.001)
				Critical	32 (16/16)	69 (61, 83)	69 (48, 81) mg/dL	

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…continuation of Table 3.

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
								Significantly lower LDL-c levels in severe COVID-19 patients compared to mild patients (p< 0.02) Significantly lower LDL-c levels in critical COVID-19 patients compared to severe patients (p< 0.001) Significantly lower LDL-c levels in critical COVID-19 patients compared to severe patients (p< 0.001)
Xie et al. (2020)	Department of Infectious Disease at the Cancer Center, Union Hospital of Tongji Medical College, Huazhong Science and Technology in Wuhan, China	Cross-sectional study	All PCR-confirmed COVID-19 patients	All Severity	62 (27/35)	66.0 (53.3, 73.0)	2.2 (1.9, 2.5) mmol/L	No significant difference in LDL-c levels between severe and non-severe COVID-19 patients with CVD (p= 0.652)
				Non-Severe With CVD	16 (4/12)	66.0 (56.3, 73.0)	2.2 (1.9, 2.6) mmol/L	
				Without CVD	22 (10/12)	58.0 (42.8, 66.3)	2.2 (2.0, 2.3) mmol/L	
				Severe	17	73.0	2.2 (1.8, 3.4)	No significant difference in LDL-c levels

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…continuation of Table 3.

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
				With CVD	(8/9)	(64.5, 83.0)	mmol/L	between non-severe COVID-19 patients with and without CVD (p= 0.636) No significant difference in LDL-c levels between severe COVID-19 patients with and without CVD (p= 0.401)
				Without CVD	7 (5/2)	69.0 (51.0, 75.0)	2.5 (1.9, 3.5) mmol/L	
G. Wang et al. (2020)	Public Health Treatment Center of Changsha, China	Case-control study	All PCR-confirmed COVID-19 patients	Control	1 140 (575/565)	45.5 (36.0, 60.8)	2.83 (2.27, 3.39) mmol/L	Significantly lower LDL-c levels in all COVID-19 patients compared to control (p< 0.001)
				All Severity	228 (115/113)	45.5 (36.0, 60.8)	2.63 (2.21, 3.09) mmol/L	
				Non-Severe	184	N/A	2.65 (2.22, 3.10) mmol/L	No significant difference in LDL-c levels between severe and non-severe COVID-19 patients (p= 0.233)
				Severe	44	N/A	2.60 (2.19, 2.95) mmol/L	

* Sample size are presented in total patients (male/female)
† Age of patients are presented as years in median (interquartile range [IQR]) or mean ± SD
** Serum LDL-c levels are presented in median (interquartile range [IQR])
Note. COVID-19 = Coronavirus Disease 2019; CVD = Cardiovascular Disease; LDL-c = Low-Density Lipoprotein Cholesterol; N/A = Not Available; NS = Not Significant; PCR = Polymerase Chain Reaction.

no significant difference in serum LDL-c levels between severe and non-severe COVID-19 patients. A study by Xie et al. (2020) found that in COVID-19 patients with cardiovascular disease (CVD), serum LDL-c levels were also not significantly different between severe and non-severe groups. The summary of these findings in this study showed that serum HDL-c levels may serve as a better severity predictor in COVID-19 patients than serum LDL-c levels.

The risk of bias using the NOS score was presented in Table 4 and Table 5. All of the included studies were good-quality studies or at low risk of bias.

Table 4

Risk of Bias Assessment of Case-Control Studies Using Newcastle-Ottawa Scale (NOS) Score

NOS Score of Case-Control Study	**Hu et al. (2020)**	**Wei et al. (2020)**	**G. Wang et al. (2020)**
Selection			
Is the case definition adequate?	*	*	*
Representativeness of the cases	*	*	*
Selection of controls	0	0	0
Definition of controls	*	*	0
Comparability			
Study controls for serum HDL-c and LDL-c levels	*	*	*
Study controls for other factors	*	*	*
Exposure			
Ascertainment of exposure	*	*	*
Same method for ascertainment for cases and controls	*	*	*
Non-response rate	*	*	*
Total Score	8	8	7
Interpretation	L	L	L

Note. L = Low risk of bias or good-quality study; NOS = Newcastle-Ottawa Scale.

Table 5

Risk of Bias Assessment of Cross-Sectional Studies Using Newcastle-Ottawa Scale (NOS) Score

NOS Score of Cross-Sectional Study	**Zhang et al. (2020)**	**Shu et al. (2020)**	**D. Wang et al. (2020)**	**Xie et al. (2020)**
Selection				
Representativeness of the sample	*	*	*	*
Sample size	*	*	*	*
Non-respondents	*	*	*	*
Ascertainment of exposure (risk factors)	*	*	*	*
Comparability				
Comparability of subjects in different outcome groups on the basis of design or analysis (data adjustment for confounding factors)	0	0	0	0
Exposure				
Assessment of outcome	**	**	**	**
Statistical test	*	*	*	*
Total Score	7	7	7	7
Interpretation	L	L	L	L

Note. L = Low risk of bias or good study; NOS = Newcastle-Ottawa Scale.

DISCUSSION

We found that low serum HDL-c levels are associated with severe COVID-19 cases, while serum LDL-c levels are not associated with COVID-19 severity. HDL-c is a beneficial lipoprotein in the human body, which consists of triglycerides, cholesterols, and several lipoproteins (Apo-AI, Apo-AII, Apo-AIV, Apo-AV, Apo-C1, Apo-CII, Apo-CIII, and Apo-E) (17). There was a change in the plasma HDL-c levels at the time of viral infections, including human immunodeficiency virus (HIV) and HCV infections. Scavenger receptor class B type I (SR-BI), a protein that took part in the HDL-c life cycle, was known for having a vital role in the HCV infection. Whilst, HIV could modulate the systemic inflammation by decreasing the antioxidant and anti-inflammatory activities due to the transformation of HDL-c to pro-oxidant and pro-inflammatory acute phase HDL-c (18). Although the mechanism of HCV and HIV in decreasing the HDL-c levels have been established, this mechanism remained unclear in SARS-CoV-2 infection. However, several hypotheses stated that the mechanism for the declining of HDL-c levels during COVID-19 was similar to HIV-1 infection. Both shared a similar relationship for the viral infection in the HDL-c and cholesterol pathways. An in vitro investigation of SARS-CoV-2 infection reported that cholesterols were needed in two checkpoints of the SARS-CoV life cycle and took part in the early stage of the viral replication and its binding while penetrating the host cells (12).

HDL-c also has a beneficial function in protecting the host from several diseases, including viral pneumonia. Despite its role as an anti-inflammatory agent, the inflammatory process in infection may alter the HDL-c structure and produce the acute phase serum amyloid A (SAA) protein. SAA could reduce the anti-inflammatory function of HDL-c and further induce the pro-inflammatory condition by activating the macrophages and translocating toll-like receptor 4 (TLR4) into the lipid rafts. As a result, those will decrease the serum HDL-c levels and increase the serum total cholesterol-to-HDL-c (TC/HDL-c) ratio. Those processes were observed in community-acquired pneumonia (CAP) patients, especially viral pneumonia (7,12). Furthermore, a study by G. Wang et al. (2020) also showed that COVID-19 patients with low serum HDL-c levels (<0.65 mmol/L or <25 mg/dL) had significantly higher levels of C-reactive protein ($p<0.001$) compared to high serum HDL-c levels and caused two to three times higher risk of developing severe events in COVID-19 ($p = 0.019$; HR [95 %CI] = 2.827 [1.190-6.714]) (13). Moreover, in COVID-19, HDL-c was bound to the spike protein of SARS-CoV-2. This binding mechanism was inhibited by SR-BI, a receptor that antagonists the activity of HDL-c, through its function on transferring HDL-c back to the liver. However, this protective mechanism was overly active, and instead, it reduced serum HDL-c levels in COVID-19 patients (7). Overall, serum HDL-c levels will drop following the severity of COVID-19. These mechanisms supported our study result: 6 of 7 included studies showed that severe COVID-19 tend to have lower serum levels of HDL-c compared to the non-severe group. Although the levels of HDL-c were correlated with the COVID-19 severity, advanced studies on the role of HDL-c in SARS-CoV-2 infection still needed further investigations.

LDL-c is one of the lipoprotein particles, other than HDL-c, that support the cholesterol distribution in the body. Although LDL-c and HDL-c are formed by similar particles, both have different characteristics. LDL-c was related to the increased risk of atherosclerotic lesion formation, while HDL-c was inversely correlated with this event (19). However, both shared a similar role in combatting infections by neutralizing the bacterial lipopolysaccharides (LPS). Furthermore, some observational studies showed that the LDL-c concentration could decrease up to 30 % during an inflammatory state in sepsis. Low LDL-c concentration could also act as a predictor of sepsis severity (9). Lipids also played an important role in infection, including viral infection. Several types of the virus could use the lipid components as their receptor. *Flaviviridae*, such as HCV and Bovine Viral Diarrheal Virus (BVDV), were known for their involvement in affecting the LDL-c concentration by penetrating the host cells through the LDL receptor (LDL-R) (20). Interaction between low affinity-LDL-Rand HCV was required for an early virion attachment. Dengue virus

also disturbed and altered the patients' lipid profiles, including the total cholesterol (TC) and lipoprotein, especially LDL-c (9,20).

In SARS-CoV-2 infection, the patients' lipid profiles, including HDL-c, LDL-c, and TC, were lower than the healthy controls due to the disturbance in the lipid transfers process. ARDS in COVID-19 could also decrease the lipoprotein levels. While the role of HDL-c in its infection has been hypothesized in the acute phase through the involvement of SAA and SR-BI, the role of LDL-c was still poorly understood (9). The existing hypothesis was explained as follows: LDL-c will be oxidized into oxLDL, which increases the SARS-CoV-2 infection rate by activating the oxLDL-specific scavenger receptor called lectin-like oxLDL receptor (LOX-1). Then, LOX-1 stimulates the intracellular signaling process to produce pro-apoptotic, pro-oxidant, and pro-inflammatory states, resulting in cell dysfunction, atherosclerosis, and CVD. Of this process, the role of LOX-1 was crucial in causing complications in COVID-19 (11). As the consequences, the serum LDL-c levels could fall as shown by Hu et al. (2020), Wei et al. (2020), and G. Wang et al. (2020) in our study, which provided proof of significantly lower LDL-c levels in all COVID-19 patients regardless of the severity, compared to control. However, our study also showed that serum LDL-c levels were not significantly different between severe and non-severe COVID-19 patients in 5 (71.42 %) of the included studies. This contrast finding could be explained by the lower number of COVID-19 patients in each of those studies compared to each of the two other studies stating the opposing result. Finally, based on our study, although the latter role of LDL-c in SARS-CoV-2 infection seemed to be promising in affecting the disease severity, its actual role and mechanism still remained questionable and needed further investigation due to the lower number of evidence as compared to HDL-c (10,12,13).

There are few limitations in this systematic review. First, the majority of the included studies (85.71 %; n= 6) did not provide any odds ratios (ORs) of the analyzed outcomes and were just limited to the p-value. Second, the quantitative analysis was not conducted in this study due to the absence of the mean and standard deviation (SD) data of serum HDL-c and LDL-c levels in all of the included studies. Third, the authors' comprehensions are limited to the English language as stated in the exclusion criteria. Thus, we recommend future studies to evaluate the ORs, mean, and SD to provide future systematic review and meta-analysis in updating the roles of serum HDL-c and LDL-c levels as the potential predictor of the disease severity of COVID-19.

CONCLUSION

We found that low serum HDL-c levels are associated with severe COVID-19 cases, while serum LDL-c levels are not associated with COVID-19 severity. Therefore, serum HDL-c levels may serve as a better predictor of the COVID-19 severity than serum LDL-c levels. We also suggest future studies to further assess, establish, and strengthen the evidence of this potential marker of the disease severity in the COVID-19 era.

Conflict of Interest

All of the authors had no conflict of interest.

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Correlation of HbA1c levels and diabetic neuropathy complications in diabetes mellitus patients

Correlación de niveles de HbA1c y complicaciones de neuropatía diabética en pacientes con diabetes mellitus

Anisatul Hamida[1*], Laily Irfana[2*•], Detty Nur Irawati[3*]

SUMMARY

Introduction: *Type 2 Diabetes Mellitus (DM) is a metabolic disease caused by impairments in insulin secretion by pancreatic beta cells and/or impaired insulin regulation by the body (insulin resistance). Inadequate management of DM can be a trigger of several complications, such as diabetic neuropathy. This study aims to prove the correlation between HbA1c levels and the occurrence of diabetic neuropathy.*
Methods: *This research was a cross-sectional study. The researchers collected HbA1c data of patients who had conducted their HbA1c test maximally over the past month through medical records. They were examined by Diabetic Neuropathy Examination (DNE) scores and asked about their complaints by Diabetic Neuropathy Symptoms (DNS) scores.*
Results: *This study involved 40 respondents who were patients with DM. Most of the respondents with DM were male (52.5 %), elderly (77.5 %), and uncontrolled HbA1c (72.5 %). The analysis of the correlation of HbA1c levels and diabetic neuropathy using the Spearman test showed a quite strong correlation (p=0.001). Patients with HBA1C in an uncontrolled category were 22.73 (1/0.044) times more at risk than in a good category.*
Conclusion: *Uncontrolled HbA1c levels had a higher risk of diabetic neuropathy complications than the controlled group.*

Keywords: *HbA1c, diabetic neuropathy, diabetes mellitus.*

RESUMEN

Introducción: *La diabetes mellitus (DM) tipo 2 es una enfermedad metabólica causada por alteraciones en la secreción de insulina por las células beta pancreáticas y / o alteración de la regulación de la insulina por parte del organismo (resistencia a la insulina). El manejo inadecuado de la DM puede desencadenar varias complicaciones, como la neuropatía diabética. Este estudio tiene como objetivo probar la correlación entre los niveles de HbA1c y la aparición de neuropatía diabética.*

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Métodos: *Esta investigación fue un estudio transversal. Los investigadores recopilaron datos de HbA1c de pacientes que habían realizado su prueba de HbA1c al máximo durante el último mes a través de registros médicos. Fueron examinados mediante las puntuaciones del Examen de neuropatía diabética (DNE) y se les preguntó acerca de sus quejas mediante las puntuaciones de los Síntomas de neuropatía diabética (DNS).*
Resultados: *Este estudio involucró a 40 encuestados que eran pacientes con DM. La mayoría de los encuestados con DM eran hombres (52,5 %), ancianos (77,5 %) y HbA1c no controlada (72,5 %). El análisis de la correlación de los niveles de HbA1c y la neuropatía diabética mediante la prueba de Spearman mostró una correlación bastante fuerte (p= 0,001). Los pacientes con HBA1C en una categoría no controlada tenían 22,73 (1 / 0,044) veces más de riesgo que en una buena categoría.*
Conclusión: *Los niveles de HbA1c no controlados tenían un mayor riesgo de complicaciones de la neuropatía diabética que el grupo controlado.*

Palabras clave: *HbA1c, neuropatía diabética, diabetes mellitus.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that does not cause immediate death but can be fatal if improperly managed (1). DM and hypertension are the two highest non-communicable diseases (2,3). Type 2 DM is a metabolic disease caused by an impairment in insulin secretion by pancreatic beta cells and/or impaired insulin regulation by the body (insulin resistance) (1). Several lifestyle factors are known to increase the risk of Type 2 DM, including lack of physical activity, unhealthy diet, and obesity (4). DM causes complications, including acute- and chronic complications (5). An inappropriate DM management causes a patient's glucose levels to be uncontrolled (6). Hence, it can provoke several complications like diabetic neuropathy, which becomes the most common complication in DM. DM patients have 11 times riskier of developing neuropathy compared to those without diabetes (7).

The prevalence of DM in the world continues to rise, particularly in developing countries, including Indonesia, which requires serious attention (8). According to the WHO, diabetes mellitus patients in Indonesia have increased from 8.4 million in 2000 to 13.7 million in 2003 and are expected to reach approximately 21.3 million by 2030. According to the International Diabetes Federation's (IDF) most recent survey, 382 million people worldwide suffered from diabetes in 2013. By 2035 those numbers are estimated to increase, becoming 592 million. In 2017, diabetic patients in the world will rise to 425 million, and it is predicted that by 2045 it will increase to 629 million (3-5). In 2017, Indonesia was in the sixth rank of people living with diabetes in the world with 10.3 million and will be projected to rise to 16.7 million in 2045 (9).

Diabetic neuropathy can be caused by a variety of different biochemical changes, the most significant of which is chronic hyperglycemia. Axonal injury associated with hyperglycemia, insulin resistance, toxic adiposity, endothelial injury, and microvascular dysfunction may result in nerve ischemia and lead to the development of neuropathy. Additionally, neuropathy develops as a result of changes in vascular conditions, neurostructural pathways, and metabolic interactions. Changes in sodium and calcium channel distribution and expression, altered neuropeptide expression, peripheral sensitization, altered blood flow, axonal atrophy, small fiber injury, glycemic flux, increased peripheral nerve epineural blood flow, altered foot skin microcirculation, increased thalamic vascularity, and autonomic dysfunction is all examples of metabolic interactions. Those are factors affecting diabetic neuropathy and its development (10). Furthermore, in hyperglycemia, much glucose enters the polyol pathways so that many aldose reductase enzymes are used to convert glucose to sorbitol. This condition can generate the reduction of glutathione and NO due to the use of NADPH. It can make the nerve cells more sensitive to oxidative stress, which causes nerve damages (11).

Hyperglycemia in DM can be prevented and controlled by good glycemic control and treatment. The evidence says that only strict and monitored glycemic control can reverse and prevent neuropathy. Microvascular complications are probably able to occur due to poor glycemic controls so that a marker for impaired glycemic control is needed to be a potential predictor in assessing DM complications. Therefore, checking

HbA1c up over several months is probably reliable to find out the glycemic variability of a person in a long term (12). HbA1c is a type of hemoglobin A which compounds with sugar in the blood, so its concentration depends on the age of erythrocytes and blood sugar. That is 120 days. The HbA1c will decompose simultaneously as its final period; thus, the HbA1c test is conducted every 2-3 months (13). Thereby, hyperglycemia can be detected by the HbA1c test. Someone with poor glycemic control will cause uncontrolled hyperglycemia, so the number of glucose in polyol pathways, which should be low, will be high instead (14).

Some researchers mentioned that HbA1c levels have positive correlations to diabetic neuropathy levels. However, the others argued that no significant correlations were found between them. This study purposed to prove the correlation between HbA1c levels and the occurrence of diabetic neuropathy.

METHODS

This study used an observational research design with the cross-sectional approach. It was conducted at Siti Khodijah Hospital, Sepanjang, Sidoarjo, Indonesia. The sample used in the study was DM patients both inpatients and outpatients in the hospital. The sampling technique was simple random sampling. The inclusion criteria in this study were DM patients who had data from the result of the HbA1c test and had conducted the test maximally over the past month. While the exclusion criteria were DM patients with a medical history of iron deficiency anemia, polycythemia rubra vera, second-trimester pregnancy, high blood urea levels, severe hypertriglyceridemia, hyperbilirubinemia, excessive alcohol consumption, splenectomy, aplastic anemia, and long-term use of high doses of salicylates.

To diagnose diabetic neuropathy in accordance with the San Antonia consensus, this study used the Diabetic Neuropathy Symptom (DNS) Score and the Diabetic Neuropathy Examination (DNE) score. DNS score is a score containing 4 points to assess neuropathy symptoms: (1) unsteadiness on walking (2) pain during walking (3) tingling in the legs or feet (4) numbness in the legs or feet. It has a sensitivity of 64.41 % and a specificity of 80.95 %. DNE score is a scoring system to diagnose polyneuropathy in DM. It has a sensitivity of 96 % and a specificity of 51 %. Its score consists of 1) Quadriceps Femoris test (Extension of the knee joint), 2) Tibialis anterior (Foot Dorsiflexion), 3) Achilles Reflex, 4) Index finger (against puncture), 5) Big toe (against puncture), 6) Touch sensitivity, 7) Vibration sensation, 8) Perception of joint position. Those instruments have been tested many times and the results can diagnose neuropathy. The research procedure was conducted by recording HbA1c data of DM patients who had checked maximally over the past month, after that they were examined by DNE score and asked about their complaints by DNS score. Data analysis was conducted by the Spearman test and afterward performed by binary logistic regression.

RESULTS

This study involved 40 respondents who were patients with DM. The information collected were sex, age, and HBA1C examination results from respondents described in Table 1. Most of the respondents with DM were male, elderly, and uncontrolled HbA1c.

Table 1

Respondents' Characteristics

Characteristics	Frequency	Percentage
Sex		
Male	21	52.5
Female	19	47.5
Age (Year)		
<50	9	22.5
>50	31	77.5
HbA1c		
Good Status	6	15.0
Intermediate Status	5	12.5
Uncontrolled	29	72.5
Total	40	100.0

Table 2 shows that most respondents with uncontrolled HbA1c are 29 patients (72.5 %). The results of the Spearman correlation test showed that the contingency coefficient was 0.534, and the p-value was 0.001 (<0.01).

Table 2

Correlation coefficient of HBA1C on the occurrence of diabetic neuropathy complications

Levels of HbA1c	n	Percentage	p
Controlled/ Good	6	15.0	
Intermediate	5	12.5	
			0.000
Uncontrolled	29	72.5	
Total	40	100.0	

Spearman Test Results Correlation coefficient = 0.534

A binary logistic regression test was carried out to know the tendency to experience complications of diabetic neuropathy, and a simultaneous test was carried out, a model fit test (goodness of fit), partial test, and odds ratio (OR). The simultaneous test results using the omnibus test with null hypothesis showed no independent variables that affect the occurrence of complications of diabetic neuropathy (p= 0.020). The results of the model suitability test using the Hosmer and Lemeshow test, with the null hypothesis the model used was appropriate or suitable to explain the relationship between the independent variable and the dependent variable (p= 0.550). Based on Table 3, the partial test and nods ratio results using the Wald Test with the null independent variable hypothesis do not affect the occurrence of complications of diabetic neuropathy.

Table 3

Partial Test Results and Odds Ratio

Variable	β	S.E.	Wald	df	P-value	Exp (β)
Checked Status			8.272	2	0.016	
Checked Status (1)	-3.115	1.251	6.195	1	0.013	0.044
Checked Status (2)	-1.954	1.041	3.522	1	0.061	0.142
Age Category	0.227	1.030	0.049	1	0.825	1.255
Sex	-0.077	0.816	0.009	1	0.925	0.926
Constant	1.412	1.085	1.694	1	0.193	4.106

DISCUSSION

This research discussed the correlation between HbA1c levels and diabetic neuropathy. There was a relatively strong and significant correlation between HbA1c levels and diabetic neuropathy. It was according to a study conducted by United Kingdom Prospective DM Study (UKPDS), which declared that the higher the HbA1c value in DM patients, the more potential complications would occur (7). The previous study also affirmed that there was a correlation between HbA1c levels and nerve damage. Patients with HbA1c ≥ 8 had 3.13 times higher risk of nerve damage (14).

In this study, the Odds Ratio test was also carried out to see how much the independent variable affected the dependent variable and the HbA1c variable with good status was 0.044. This means, uncontrolled HbA1c has the risk to suffer from diabetic neuropathy complications was 22.73 (1/0.044) times greater than those who were in a good category. In line with the previous report, which stated that the result of HbA1c levels significantly increases the risk of diabetic peripheral neuropathy (NDP) by 4.82 times compared to DM patients with normal HbA1c (13).

The statement above can be explained by the polyol pathway and AGE's theory. HbA1c is the binding of hemoglobin with glucose in the body in the last 2-3 months, so its levels indicate high glucose levels in the blood. HbA1c and blood glucose levels are directly related because erythrocytes continuously glycated for 120 days,

and the rate of formation glycohemoglobin is equivalent to the concentration of blood glucose. Hence, hyperglycemia can be detected by an HbA1c examination.

This hyperglycemia condition can cause metabolic disorders in one or more of the nerve cell components. In hyperglycemia, large amounts of glucose enter the polyol pathway, using the aldose reductase enzyme to convert the glucose to sorbitol; consequently, many NADPH is consumed. This situation causes the reduction of glutathione and NO, so the nerve cells become more sensitive to oxidative processes. On top of that, the excessive glucose in the body will compound to non-enzymatic amino protein acids and then glycosylated. This glycosylation will produce the final result in the form of Advance Glycation End Products (AGEs). Schwann cells, nerve fibers, and endothelial cells of the vasa nervosum show RAGE in the nervous tissue. The AGE production will link to RAGE, which is revealed by several nerve cells; thus, an oxidative stress reaction is formed through the activation of NADPH oxidase. Ultimately, microangiopathy and nerve dysfunction occur, leading to pain or delaying nerve conduction (11).

Additionally, this study examined the relationship between neuropathy and sex and age. The findings for sex indicate no meaningful association existed between age and diabetic neuropathy. This is consistent with a study that found a correlation between age and diabetic neuropathy of p= 0.540, suggesting that there is no important correlation between age and diabetic neuropathy (15). Meanwhile, sex analysis has no significant correlation with the incidence of diabetic neuropathy. This result corroborated a previous study indicating that there is no statistically relevant association between sex and neuropathy (15).

This study has limitations. First, the duration of suffering from diabetes was a lack of attention in taking samples. Second, the theory described that the duration of suffering could affect the occurrence of complications. Third, the number of samples which is not too large also becomes a limitation in this study. Additionally, an unbalanced sex distribution can influence the results of the study as well. We suggest for the following study is about the diagnosis. The diagnosis can use electroneuromyography (ENMG), the gold standard for establishing a neuropathy diagnosis.

CONCLUSION

HbA1c levels were significantly associated with diabetic neuropathy. The correlations that occurred were positively correlated, which means that the greater the patient's HbA1c, the more significant possibility of neuropathy will be experienced. Patients with uncontrolled HbA1c status had 22.72 times of chance of running into neuropathy complications than those with a good control status.

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The proper use of face mask during COVID-19 pandemic in urban community

El uso adecuado de la mascarilla durante la pandemia de COVID-19 en la comunidad urbana

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SUMMARY

Background: *We need to know the understanding and behavior of the people for the prevention of coronavirus transmission. The breakthrough method is needed to be able to evaluate health problems among the society, provide solutions and simultaneously evaluate the impact of changes on society. This study aimed to find the problems that arise in wearing face masks during the COVID-19 pandemic, conduct educational interventions, and evaluate the results.*
Methods: *We started this study by distributing surveys to urban communities that are relatively mobile and require the use of face masks in their activities. To evaluate the changes in knowledge and behavior of respondents that lead to improvement, we did a pre-test and a post-test and evaluate the gain of the test score.*
Results: *266 respondents filled out the online survey. There are 79.3 % of respondents wear reusable masks, 24.8 % choose the wrong mask material. There are still 2.8 % of respondents who wear their masks continuously and never change them and 19.5 % of respondents did not wash their reusable masks before putting them back on. some still dispose of mask waste mixed with household waste. the results of the*

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test evaluation showed an increase in gain before and after providing educational materials online.
Conclusion: The public health intervention provided via online education shows the better changes, both in knowledge or behavior from respondents who represent the urban communities.

Keywords: *Behavior, COVID-19, e-community intervention, face mask, knowledge, proper use.*

RESUMEN

Antecedentes: *Se requiere conocer la comprensión y el comportamiento de las personas en la prevención de la transmisión del coronavirus. Es necesario el método innovador para poder evaluar los problemas de salud en la sociedad, brindar soluciones y, simultáneamente, evaluar el impacto de los cambios en la sociedad. Este estudio tiene por objetivo encontrar los problemas que surgen en el uso de mascarillas durante la pandemia de COVID-19, realizar intervenciones educativas y evaluar los resultados.*
Métodos: *Este estudio se inició distribuyendo encuestas a comunidades urbanas que son relativamente móviles y requieren el uso de máscaras faciales en sus actividades. Para evaluar los cambios en el conocimiento y el comportamiento de los encuestados que conducen a la mejora, se hizo una prueba previa y una prueba posterior, y se evaluó la ganancia de la puntuación de la prueba.*
Resultados: *266 encuestados completaron la encuesta en línea. El 79,3 % de los encuestados usa máscaras reutilizables, el 24,8 % elige el material de máscara incorrecto. Todavía hay un 2,8 % de los encuestados que usan sus máscaras continuamente y nunca las cambian y el 19,5 % de los encuestados no lavaron sus máscaras reutilizables antes de volver a ponérselas. Algunos todavía eliminan los desechos de las mascarillas mezclados con los desechos domésticos. Los resultados de la evaluación de la prueba mostraron un aumento en la ganancia antes y después de proporcionar materiales educativos en línea.*
Conclusión: *La intervención de salud pública proporcionada a través de la educación en línea muestra los mejores cambios, tanto en el conocimiento como en el comportamiento de los encuestados que representan a las comunidades urbanas.*

Palabras clave: *Comportamiento, COVID-19, intervención e-comunidad, mascarilla, conocimiento, uso adecuado.*

INTRODUCTION

At the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, the use of face masks has become a common sight in many countries all around the world. Required to wear a face mask to prevent transmission of the corona 2 virus. Many experts believe that the main route of transmission for SARS-CoV-2 is most likely through respiratory droplets spreading when someone speaking, coughing, or sneezing. The droplet is very tiny particel with average sizes ranged from 5 μm to 10 μm (1,2). However, there is still no agreement as to whether the transmission is through the aerosol route

The Indonesian Task Force for COVID-19 (2020) statement release that most Indonesian people have already used a face mask, in fact, the number of new cases still rising (3). This may be due to the way they use the face mask. It is probably they used the masks improperly. The material of the mask also has a contribution to preventing the virus from spreading. The fact is using the face mask correctly will decrease the possibility of droplet infection. On the other hand, when every person followed the rules to wear a face mask, it will cause face mask waste which needs a special way to treat those waste.

Base on those facts, we conducted this community-based study. In this study, we aim to find patterns and found the problems in the use of face masks during the COVID-19 pandemic in the community. Make an educational intervention for the problems, and proceed with evaluate the changes after the intervention.

METHODS

This is a descriptive study that aims to find health problems among the community, provide solutions by giving education, and monitor changes in the level of understanding and behavior a few weeks later. All of these activities were carried out online because it was carried out during the COVID-19 pandemic. We started this study by conducting a virtual survey of random respondents in urban areas (Figure 1). From this

survey, we will get an overview of the various health problems that exist in the population. based on the existing problems, we will conduct various virtual education to solve those problems by the virtual educating system. We will evaluate the expected behavior changes 2 weeks after we provide the virtual education. The questioner variables are the knowledge for the proper use in using a face mask and correct mask processing. The questioner variables are the knowledge for the proper use in using a face mask and correct mask processing. The proper face mask evaluation includes a cognitive knowledge assessment for all matters related to the correct way of wearing masks. Questioner for processing correct mask includes the cognitive assessment of related how to process the masks properly.

The distribution of questionnaires was conducted online by medical students who were currently studying community medicine. The target population was students, private employees, and government employees. This community was chosen because basically they already have personal gadgets and are aware of technology.

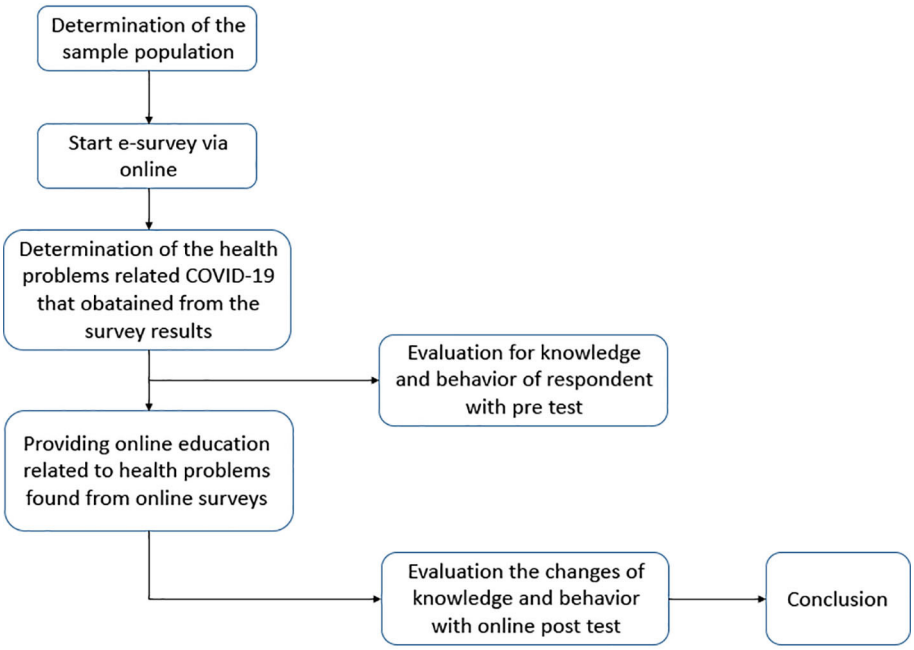

Figure 1. Schematic for online survey and health intervention.

The proper face mask evaluation includes a cognitive knowledge assessment for all matters related to the correct way of wearing masks. Questioner for processing correct mask includes the cognitive assessment of related how to process the masks properly. To evaluate changes in knowledge and behavior of respondents after intervention with virtual education, we conduct pre-tests and post-tests, to then assess changes in the score test. The post-test was carried out 3 weeks after giving virtual education so that we could evaluate the changes in the daily behavior of the respondent.

RESULTS

The age distribution group of respondents seems to be dominated by the student and young

workers age group, followed by the school-age group (Figure 2). It makes sense that this dominated group are those who were active with their gadget and using online information a lot. The initial questionnaire that was followed by 266 respondents consists of 92 (34.5 %) males and 174 (65.5 %) females (Figure 3). There are 211 (79.3 %) respondents who used reusable masks (Figure 4). The most widely used mask materials were propylene (68 respondents) 25.5 %, woven cotton cloth (66 respondents) 24.8 %, polyester / scuba material (63 respondents) 23.6 %, and the least used was knitted fabric (33 respondents) 12.4 % and other materials (46 respondents) 17.2 % (Figure 5). They used a face mask that consisted of 3 layers (18.9 %), 2 layers (42.7 %), and 1 layer (38.4 %). The average duration of reusable masks by respondents is quite good, it can be seen that 50.7 % of respondents change their masks daily, and the rest are about 2-3 days on average change their face mask. But there are still 2.8 % of respondents who never even

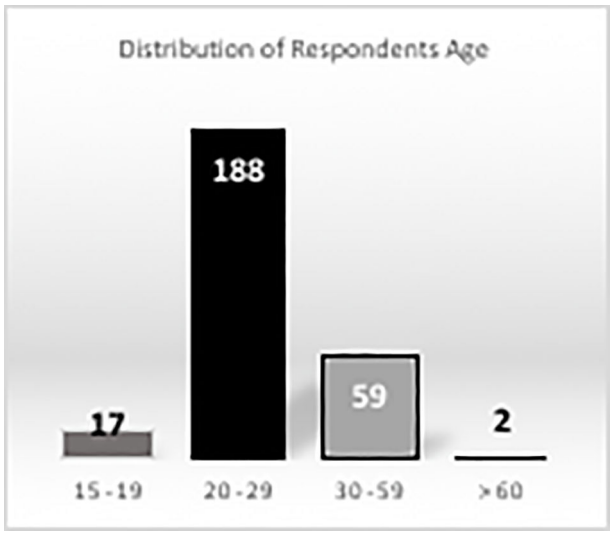

Figure 2. Age distribution of Respondents.

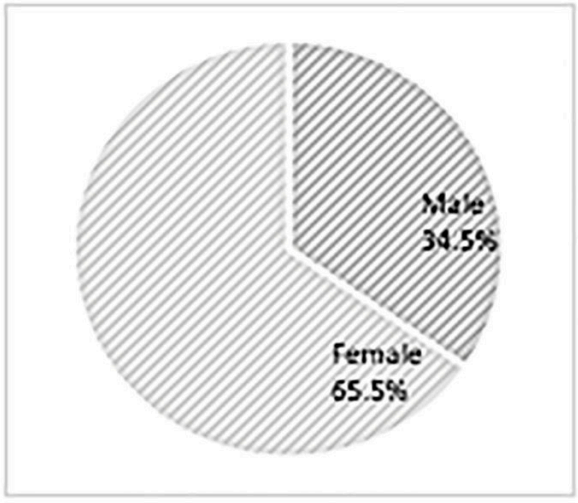

Figure 3. Sex distribution of Respondents.

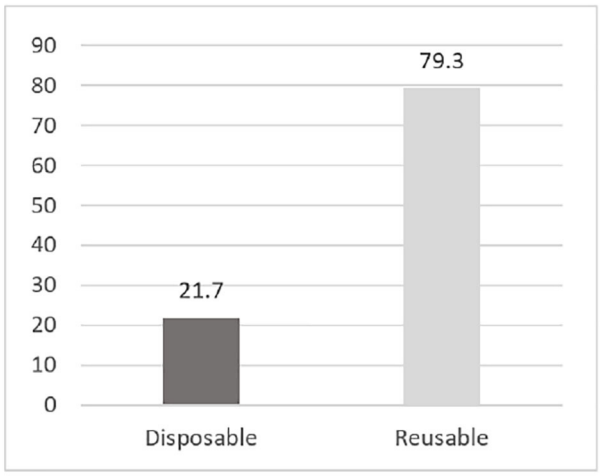

Figure 4. Type of Mask precentage.

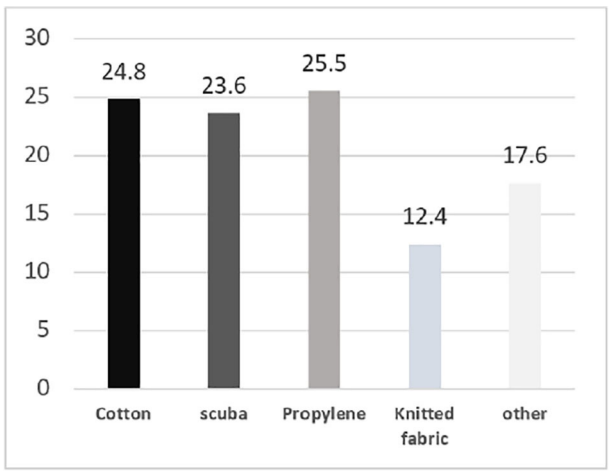

Figure 5. Type of Mask Material precentage.

change their masks. Before re-using the mask, 80.5 % of respondents decided to wash their masks first, the others chose to dry, hang, and wear new masks. but, 4.2 % of respondents did nothing to their masks.

The questionnaire results concluded that there are major problems in the community regarding the use of masks. There is still a lack of public knowledge about the proper use of masks and a lack of public knowledge regarding properly used mask waste management. Based on the main problems from the questionnaire, we provide e-education online with the subject of the purpose of wearing face masks. This education also discusses when is the right time to wear a face mask, the types of face masks based on the material, the layer, and how to wear a face mask properly. Education for waste treatment contains how to properly manage the used-mask waste according to the guidelines of the Ministry of Health of the Republic of Indonesia which are adapted from WHO guidelines.

After getting the educational material, we invited the respondents to do the pre-test. There were 266 respondents, 112 respondents were willing to fill in the pre-test. but after 3 weeks later we asked to fill out a post-test to evaluate changes in behavior from the respondents, we found 44 respondents who were willing to fill out the post-test. thus, we evaluated 44 respondents who had different gains to assess the presence of behavior change after intervention through e-education.

Table 1

Evaluation results of knowledge and behaviour of respondents

	Respondents	Percentage of complete test (%)	Mean scoring	Median scoring
Pre-Test	44	100	4.61	5 (0-10)
Pos-Test	44	100	8.47	9 (5-10)

There was a significant change in pre and post-test results which showed changes in both knowledge and behavior of the respondents, especially regarding the use of mask and processing its limbs correctly.

DISCUSSION

The main role of public health during an outbreak is to understand transmission in terms of time, place, and sufferers to then identify risk factors for disease to determine targeted interventions so that they will be more effective (4,5). The condition of the COVID-19 pandemic has required the role of digital technology both for data collection and for evaluating a policy quickly set by policymakers. Targeted coping strategies are likely to require rapid and complex coordination. Collaboration and coordination are not only at the level of policymakers but are needed between various components of government, regulators, the private sector, the community, non-governmental organizations, and sufferers. Public health has long been underfunded relative to other health funding. the use of an online data system can also be used to estimate the spread of an infectious disease in the community in real conditions (6,7).

In determining the population to be surveyed online, considering whether the topic is suitable for an online survey is the first thing to do. Likewise, efforts to minimize bias and increase the validity of survey results, as well as the size of the participation of respondents (8). In this study, we choose the urban community on the active age population because this population is the vulnerable population to get COVID-19 infection if they don't use face mask properly.

Systematic and coordinated communication with the people society is needed to maintain public trust in the capacity of the health system to provide safe and quality services (8,9). if there are no or possible meetings involving the community, then consider creating a remote digital mechanism to ensure two-way feedback for data and processing surveillance information. Make it easier for people to access and use the data they need. Information systems are also for decision making, providing feedback to the community (for example, questions and information about news, rumors, and everything about COVID-19) to then follow up based on the data obtained (9).

CONCLUSION

During the COVID-19 pandemic era, where the people, especially health workers, limited direct contact with each other according to health protocols, public health interventions could be pursued through an online system. Identification of health problems that arise in the community can be done through online surveys. This system is proven to be able to identify the health problems that arise among the community, as well as provide education on how to handle those problems, which is promotive preventive in accordance with existing problems. The community intervention provided via online education shows a significant change for the better changes, both in knowledge and changes in behavior from respondents who represent the urban communities.

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Soluble CD163 and small dense LDL cholesterol levels in type 2 diabetes patients

CD163 soluble y niveles de colesterol LDL denso pequeño en pacientes con diabetes tipo 2

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SUMMARY

Introduction: *The sdLDL cholesterol proportion is a better marker for the prediction of cardiovascular diseases (CVDs). Macrophages play a crucial role in both initiation and progression of atherosclerosis, the underlying mechanism of CVDs. This study investigated the correlation between soluble CD163 as a biomarker macrophage activation and sdLDL cholesterol in type 2 diabetes mellitus (T2DM) subjects for the first time.*
Methods: *This study was an observational analytic cross-sectional study involved 40 patients with T2DM in Surabaya, Indonesia. The sdLDL was measured using a direct enzymatic colorimetric method using Architect c8000. The levels of sCD163 were measured by a quantitative enzyme immunoassay technique using a specific monoclonal antibody for human CD163 using Quantikine® Elisa produced by R&D Systems Inc., USA.*
Results: *The average level of HbA1c in this study was 8.01 ± 1.39 %, and more than half of the subjects had HbA1c levels >8 % that revealed most of the patients in this study were in poor glycemic control. The average sdLDL cholesterol level in this study was 40.80 ± 19.14 mg/dL, and the mean of soluble CD163 was 741.22 ±41.55 ng/mL. There were no differences in gender (male or female), glycemic control (<8 % vs >8 %), hypertension, and smoking on sCD163 levels and sdLDL cholesterol levels. We found a positive correlation between the soluble CD163 level with sdLDL (r=0.440, p=0.004).*
Conclusion: *The atherogenic lipoprotein fraction sdLDL cholesterol level correlated with soluble CD163 level. This could be a new link between lipid dysregulation, innate immunity, and atherosclerosis in T2DM.*

Keywords: *sdLDL, soluble CD163, atherosclerosis, T2DM.*

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RESUMEN

Introducción: *La proporción de sdLDL colesterol es un mejor marcador para la predicción de enfermedades cardiovasculares (ECV). Los macrófagos juegan un*

papel crucial tanto en el inicio como en la progresión de la aterosclerosis, el mecanismo subyacente de las ECV. Este estudio investigó la correlación entre CD163 soluble como un biomarcador de activación de macrófagos y colesterol sdLDL en sujetos con diabetes mellitus tipo 2 (T2DM) por primera vez.

Métodos: *Este estudio fue un estudio transversal analítico observacional que involucró a 40 pacientes con DM2 en Surabaya, Indonesia. La sdLDL se midió mediante un método colorimétrico enzimático directo usando Architect c8000. Los niveles de sCD163 se midieron mediante una técnica de inmunoensayo enzimático cuantitativo usando un anticuerpo monoclonal específico para CD163 humano usando Quantikine® Elisa producido por R&D Systems Inc., EE.UU.*

Resultados: *El nivel promedio de HbA1c en este estudio fue 8,01 ± 1,39 %, y más de la mitad de los sujetos tenían niveles de HbA1c> 8 % que revelaron que la mayoría de los pacientes en este estudio tenían un control glucémico deficiente. El nivel medio de colesterol sdLDL en este estudio fue 40,80 ± 19,14 mg/dL y la media de CD163 soluble fue 741,22 ± 41,55 ng/mL. No hubo diferencias en sexo (hombre o mujer), control glucémico (<8 % vs >8 %), hipertensión y tabaquismo en los niveles de sCD163 y los niveles de sdLDL colesterol. Se encontró una correlación positiva entre el nivel de CD163 soluble con sdLDL (r= 0,440, p= 0,004).*

Conclusión: *El nivel de sdLDL colesterol de la fracción de lipoproteínas aterogénicas se correlacionó con el nivel de CD163 soluble. Este podría ser un nuevo vínculo entre la desregulación de lípidos, la inmunidad innata y la aterosclerosis en la DM2.*

Palabras clave: *sdLDL, CD163 soluble, aterosclerosis, DM2.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is related to an increase in the risk of coronary heart disease incidence, ischemic stroke, and mortality. T2DM also affects life quality by increasing the risk of heart failure, peripheral artery insufficiency, and microvascular complications. It is also affected life expectancy by decreasing about 4–8 years in patients with diabetes, compared to individuals without diabetes (1). The mechanisms of the pathogenesis of cardiovascular diseases (CVDs) in T2DM are associated with epigenetic, genetic, and cell-signaling defects in inter-related metabolic and inflammatory pathways (2). The association of T2DM and CVDs is affected by environmental factors and phenotypes of the patients. Patients with T2DM are often accompanied by other conditions such as dyslipidemia, hypertension, inflammation, procoagulant state, or thrombosis, representing risk factors for CVDs (3).

T2DM involves abnormalities in carbohydrate and lipid metabolism. Dyslipidemia is one of the comorbidities often present in patients with T2DM, which may stimulate and facilitate atherogenesis and the atherosclerosis process. Proteins help the distribution of lipids as their properties allow them to remain in the circulatory system. Those proteins are categorized according to their molecular density into very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Along with triglycerides, lipid clusters lipoproteins circulate along vessels to distal organs and tissues (3,4). LDL cholesterol plays a crucial role in the development and progression of atherosclerosis and CVD, especially in T2DM (5).

LDL consists of several subclasses with different sizes and densities of particles, including large buoyant LDL (lbLDL), intermediate LDL, and small dense LDL (sdLDL) (6). It has been well established that sdLDL has a greater atherogenic potential than other LDL sub-fractions. The proportion of sdLDL is a better predictor of cardiovascular disease than total LDL-C. The circulation time of sdLDL is longer than that of large LDL particles that are cleared from the bloodstream through the interaction with the LDL receptor. Circulating sdLDL has a lower affinity to LDL receptors, and multiple atherogenic modifications in blood plasma, such as desialylation, glycation, and oxidation, increase its atherogenicity (5,7,8). Circulating sdLDL cholesterol levels are also associated with systemic inflammation (9). Dyslipidemia and systemic inflammation, which is the leading hypothesis to explain the pathogenesis of atherosclerosis, are related to sdLDL cholesterol (10,11).

Immune system activation is associated with T2DM progression. Hyperglycemia induces an apoptotic mechanism producing inflammation in pancreatic beta cells. IL-6 stimulates apoptosis in pancreatic islets together with other inflammatory

cytokines and acts as a predictor for the progression of T2DM. Oxidative stress may also potentiate the generation of free radical oxygen and proinflammatory cytokines that disrupts and destroys the beta cells. Adaptive and innate immunity responses are involved in adipose tissue inflammation in T2DM. The phenotype switching of macrophages from predominantly anti-inflammatory M2-type to increased proportions of proinflammatory M1-type macrophages plays a critical role in the stimulation and progression of islet inflammation. The recruitment of B cells and T cells precedes adipose tissue infiltration by macrophages (12-14).

CD163 is a receptor for haptoglobin-hemoglobin complexes and is expressed solely on macrophages and monocytes. The extracellular portion of CD163 circulates in the blood as a soluble protein (sCD163) and increases acutely due to metalloproteinase-mediated cleavage near the cell membrane during inflammation and macrophage activation. The sCD163 is very useful as a biomarker of macrophage activation in various inflammatory diseases. Macrophage infiltration of adipose tissue and the liver is strongly related to the progression of T2DM (15,16). The sCD163 was associated with myocardial infarction and coronary artery disease in the population cohort (17), carotid intima-media thickness in older people (18). The sCD163 also accelerates atherosclerosis in systemic lupus erythematosus (19) and increases vulnerable plaque in human immunodeficiency virus (HIV) patients (20).

Therefore, we conduct this study to find the relationship between the sCD163 as a marker of macrophage activation and sdLDL as a predictor of CVDs risk in patients with T2DM from a tertiary referral hospital in Surabaya, Indonesia.

MATERIAL AND METHOD

Design and Population Study

This study was a cross-sectional analytic observational study that involved 40 participants with T2DM from the diabetes outpatient clinic in Dr. Soetomo general hospital, Surabaya, Indonesia. Subjects with T2DM with age more than 40 years old were recruited in the study. All subjects were on statin therapy as a part of diabetes management. Diagnosis of T2DM based on medical record or fulfilled Indonesian Society of Endocrinology Criteria 2015 (21). Subjects with acute complications of diabetes (such as ketoacidosis, sepsis, and acute infection), renal and liver impairment, chronic hepatitis, liver cirrhosis, pregnancy, HIV infection, steroid therapy, and autoimmune disease were excluded from the study. All participants gave their informed consent to participate in the study approved by the local Ethics Committee.

Data Collection

Interview and vital signs were performed in all subjects. A digital sphygmomanometer measured blood pressure (BP) after allowing the patients to rest for 15 minutes before the examination. Hypertension was defined by JNC VIII criteria (22), which subjects with systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. Weight and height were measured in all subjects, and body mass index (BMI) was calculated. The smoking status was assessed by recording the habit and duration of smoking, which active smoker was defined as the subject had >100 cigarettes during life. Blood samples were collected after an overnight fast to measure sCD163 and sdLDL cholesterol levels, biochemical variables such as triglycerides, total cholesterol, HDL, LDL cholesterol. Fasting plasma glucose, 2 hours postprandial glucose, and HbA1c levels were also measured using standard techniques. The sdLDL was measured using a direct enzymatic colorimetric method using Architect c8000. The levels of sCD163 were measured by a quantitative enzyme immunoassay technique using a specific monoclonal antibody for human CD163 using Quantikine® Elisa produced by R&D Systems Inc., USA.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation. Categorical variables were expressed as group

percentages. The mean of the group was analyzed using Student t-test analysis. The distribution of data was analyzed using the Kolmogorov-Smirnov test. Pearson's correlation was utilized to demonstrate the correlations between sCD163 and sdLDL levels if the data distribution was normal.

RESULTS

Clinical characteristic of the subjects

General characteristics of subjects such as age, sex, height, weight, BMI, and clinical features of T2DM, hypertension, and lipid profile were described in Table 1. There were 17 male and 23 female subjects. The average BMI was 25.66 ± 2.91, and the duration of diabetes was 8.13 ± 5.77 years. The average level of fasting plasma glucose was 150.20 ± 61.97 mg/dL, postprandial plasma glucose was 214.20 ± 33.64 mg/dL, and HbA1c was 8.13 ± 5.77 mg/dL. There were no different characteristics between male and female subjects in this study.

Table 1

Clinical characteristics of subjects

Characteristics	Mean ± SD		
	All (n=40)	Male (n=17)	Female (n=23)
Age (years old)	59.55 ± 8.14	60.82 ± 7.85	59.55 ± 8.14
Height (cm)	156.93 ± 7.35	162.88 ± 5.85	156.93 ± 7.35
Weight (kg)	63.20 ± 8.06	63.91 ± 8.39	63.20 ± 8.06
Body Mass Index (BMI)(kg/m^2)	25.66 ± 2.91	24.04 ± 2.37	26.86 ± 2.72
Type 2 Diabetes Mellitus			
- Duration (years)	8.13 ± 5.77	8.52 ± 5.99	7.83 ± 5.73
- Fasting plasma glucose (mg/dL)	150.20 ± 61.97	151.82± 67.44	149.00 ± 59.13
- Postprandial plasma glucose (mg/dL)	214.20 ± 33.64	227.29 ± 83.44	204.52 ± 67.39
- HbA1c (%)	8.01 ± 1.39	8.00 ± 1.50	8.02 ± 1.33
Hypertension			
- Systolic blood pressure (mmHg)	144.20 ± 20.15	145.58 ± 6.00	143.17 ± 3.43
- Diastolic blood pressure (mmHg)	87.57 ± 10.72	86.30 ± 1.88	89.29 ± 3.09
Lipid Profile			
- Total cholesterol (mg/dL)	213.20 ± 33.64	214.23 ± 24.58	212.43 ± 39.56
- LDL cholesterol (mg/dL)	145.02 ± 33.92	148.41 ± 30.21	142.52 ± 36.89
- HDL cholesterol (mg/dL)	45.25 ± 11.98	42.47 ± 7.20	47.30 ± 14.36
- Triglyceride (mg/dL)	172.07 ± 51.38	170.47 ± 44.43	173.26 ± 56.93

Soluble CD163 levels

The average levels of sCD163 in this study were 741.22 ± 41.55 ng/mL. There were no differences of gender (male or female), glycemic control (< 8 % versus > 8 %), hypertension, and smoking on sCD163 levels were found in this study (Table 2).

Small dense LDL cholesterol levels

The average levels of sdLDL cholesterol in this study were 40.80 ± 19.14 mg/dL. The sCD163 levels in this study were not affected by gender (male or female), glycemic control (<8 % versus >8 %), hypertension, and smoking (Table 3).

Table 2

Soluble CD163 level in all subjects

Variable	n (%)	Mean ± SD (ng/mL)	p
All subjects	40 (100)	741.22 ± 41.55	
Gender			
- Male	17 (42.50)	729.97 ± 64.51	0.559
- Female	23 (57.50)	749.53 ± 55.25	
Glycemic control			
- <8 %	19 (47.50)	732.64 ± 259.22	0.784
- >8 %	21 (52.50)	748.97 ± 271.03	
Hypertension			
- Yes	30 (75.00)	728.48 ± 260.56	0.522
- No	10 (25.00)	779.42 ± 277.47	
Smoking			
- Yes	7 (12.50)	634.92 ± 261.03	0.817
- No	33 (87.50)	763.76 ± 260.80	

Table 3

Small dense LDL level in all subjects

Variable	n (%)	Mean ± SD (mg/dL)	p
All subjects		40 (100)	40.80 ± 19.14
Sex			
- Male	17 (42.50)	40.87 ± 14.59	0.132
- Female	23 (57.50)	40.75 ± 22.24	
Glycemic control			
- <8 %	19 (47.50)	42.63 ± 20.74	0.412
- >8 %	21 (52.50)	39.14 ± 17.92	
Hypertension			
- Yes	30 (75.00)	39.23 ± 17.97	0.437
- No	10 (25.00)	45.52 ± 22.67	
Smoking			
- Yes	7 (12.50)	48.88 ± 22.57	0.592
- No	33 (87.50)	39.08 ± 18.27	

Correlation between soluble CD163 and sdLDL

The distribution of data was analyzed using the Kolmogorov-Smirnov test. The data distribution in this study was normal, then the correlation between sCD163 and sd LDL cholesterol levels was continued to analyze using the Pearson correlation test. There was a significant correlation between sCD163 and sd LDL cholesterol levels with p 0.004 and a correlation coefficient of 0.440 (Figure 1).

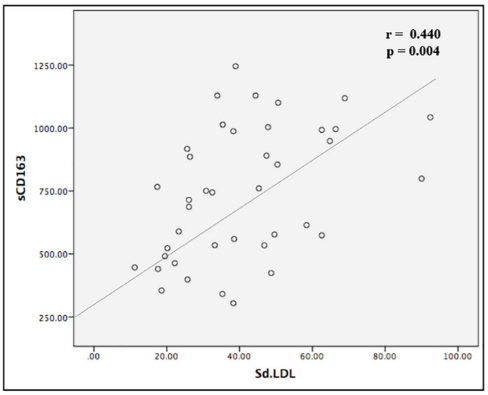

Figure 1. The correlation plot between sCD163 and sdLDL in all subjects.

DISCUSSION

We found there was a positive correlation between soluble CD163 and sdLDL in T2DM patients. The CD163 is a member of the scavenger receptor superfamily, categorized into class B, and its soluble form is a marker of activated M2 macrophages. Increased plasma levels of sdLDL were one of the predictors of atherosclerosis and cardiovascular disease in many previous studies. A positive correlation between soluble CD163 and sdLDL showed there is a link between innate immunity and the atherogenic process in the T2DM population.

Our study was also the first study that measured the soluble CD163 in the diabetes population in Indonesia. The mean of soluble CD163 levels was 741.22 ng/mL (similar to 0.741 mg/L). Although we did not have soluble CD163 data in a healthy population in Indonesia, another study in Scandinavia found that soluble CD163 levels were 0.7–3.9 mg/L in healthy individuals (16). Gender, glycemic control, hypertension, and smoking did not affect soluble CD163 levels in this study. The average level of HbA1c was 8.01 ± 1.39 %, above the target of HbA1c for T2DM. More than half of the subjects had HbA1c levels > 8 % that revealed most subjects in this study were in poor glycemic control. It was similar to the Diabcare Asia study that showed the mean levels of HbA1c in Indonesia was 8.3 ± 2.2 %, and 48.5 % of patients had HbA1c levels > 8 % (23).

Another study in subjects with type 1 diabetes mellitus, that gender did not associate with soluble CD163 levels (24), but it is different from a study in Arab Saudi, which is showed that systolic and diastolic blood pressure had an association with soluble CD163 (25). Smoking also did not give a different effect to soluble CD163 in the HIV population (26), similar to this study.

In this study, we assessed the relationship between soluble CD163 as a marker of macrophage inflammation with sdLDL as a predictor of CVD risk in the T2DM population in a tertiary referral hospital in Indonesia. This study used sdLDL cholesterol level instead of LDL cholesterol, because many individuals with LDL levels within the normal range, still develop atherosclerosis and cardiovascular disease. This implies a significant heterogeneity of LDL-particles, as the sub-fraction of small dense LDL exhibits enhanced atherogenic potential. Small dense LDL has a stronger predisposition for oxidation, lower LDL-receptor affinity, and an increased accumulation within the vascular wall (27,28). Several studies have established an association of elevated sdLDL levels with atherosclerosis and cardiovascular disease (5,7-9). The other study showed that high levels of plasma sdLDL were associated with an increased risk of major cardiovascular events among T2DM patients with coronary artery disease (29).

Monocytes and macrophages have been involved in all stages of atherogenesis, from initiation and progression to destabilization and rupture of atherosclerotic lesions. This was shown in stable coronary artery disease patients was shown there was the association of sdLDL serum levels and circulating monocyte subsets. Circulating monocytes used three distinct subtypes according to their surface expression of CD14 and CD16 (28).

During the early stages of atherosclerosis, oxidized low-density lipoproteins accumulated in the intima, stimulate the activation of endothelial cells and vascular smooth muscle cells, inducing expression and secretion of proinflammatory cytokines, and adhesion molecules that attract monocytes within the arterial wall. Monocytes continued to differentiate into the macrophages to remove oxidized LDL. There are two phenotypes of macrophages, the M1-type macrophage has a direct effect on pathogen killing, while the M2-type macrophage expresses high levels of scavenging molecules and anti-inflammatory cytokines (30). M2-type macrophages express high levels of CD163, a member of the scavenger receptor cysteine-rich family (30). The soluble form of CD163 is a normal constituent in plasma and is generated by proteolytic cleavage of CD163 at the cell surface. This receptor is now known as an immunomodulatory of atherosclerotic plaque, with anti-inflammatory and anti-atherogenic function. The soluble CD163 levels are increased in patients with atherosclerosis (28).

There were several limitations of this study that have to be considered. First, this is a single-center study from a tertiary referral hospital with a small number of patients. Second, the cross-sectional

study design only allows us to find associations between soluble CD163 and sdLDL, but could not define the causal relationship. Third, we did not differentiate subjects with CVD and non-CVD in this study. However, this study indicates a link between innate immunity and lipid metabolism in atherosclerosis-related diseases, such as T2DM.

CONCLUSION

This study gives evidence for the first time for a positive correlation between soluble CD163 as a marker of macrophage activation and atherogenic sdLDL-cholesterol levels. This result might represent a new link between an atherogenic lipoprotein phenotype and innate immunity in T2DM. Further studies are needed to understand the mechanistic relationship between macrophage activation, small dense LDL, and their specific roles in atherosclerosis-related diseases.

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Analysis of eosinophil and lymphocyte concentrations on the incidence of mild and severe acute asthma exacerbations

Análisis de las concentraciones de eosinófilos y linfocitos sobre la incidencia de exacerbaciones agudas leves y graves del asma

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SUMMARY

Introduction: *Exacerbation of asthma is an episode characterized by an increase in symptoms of progressive shortness of breath, coughing, wheezing, chest tightness, and a progressive decrease in lung function. Among the cells involved and activated in acute exacerbations in asthma are eosinophils and lymphocytes. This study aims to analyze the relationship between eosinophils and lymphocytes' concentration with the severity of acute exacerbation of asthma.*
Methods: *The method used was a cross-sectional retrospective with a sample of 40 patients with a simple random sampling technique in patients with acute exacerbation of asthma who came to the Emergency Room at Haji General Hospital, Surabaya, Indonesia.*
Results: *Patients with acute exacerbation of asthma are more dominated by women (23/40). Concurrently, the patient's age was dominated by the 46-65 age group (16/40). The conditions for discharging patients were proportionately proportional to outpatients (20/20) and inpatients (20/20). Statistical test results show the relationship of the severity of acute exacerbation of asthma with eosinophils (p= 0.003) and lymphocytes (p= 0.000). Also, a decreased trend in eosinophil and lymphocyte concentrations in severe acute asthma exacerbation compared with mild acute asthma exacerbation.*
Conclusion: *The concentration of eosinophils and lymphocytes was associated with the severity of acute exacerbation of asthma.*

Keywords: *Asthma, acute exacerbation, eosinophils, lymphocytes.*

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RESUMEN

Introducción: *La exacerbación del asma es un episodio caracterizado por un aumento de los síntomas de disnea progresiva, tos, sibilancias, opresión torácica y disminución progresiva de la función pulmonar. Entre las células involucradas y activadas en las exacerbaciones agudas del asma se encuentran los eosinófilos y los linfocitos. Este estudio tiene como objetivo analizar la relación entre la concentración de eosinófilos y linfocitos con la gravedad de la exacerbación aguda del asma.*
Métodos: *El método utilizado fue una retrospectiva transversal con una muestra de 40 pacientes con una técnica de muestreo aleatorio simple en pacientes*

con exacerbación aguda de asma que acudieron a Urgencias del Hospital General Haji, Surabaya, Indonesia.

Resultados: *Los pacientes con exacerbación aguda del asma están más dominados por mujeres (23/40). Al mismo tiempo, la edad del paciente estuvo dominada por el grupo de edad de 46 a 65 años (16/40). Las condiciones para dar de alta a los pacientes fueron proporcionalmente proporcionales a los pacientes ambulatorios (20/20) y los pacientes hospitalizados (20/20). Los resultados de las pruebas estadísticas muestran la relación de la gravedad de la exacerbación aguda del asma con eosinófilos (p= 0,003) y linfocitos (p= 0,000). Además, una tendencia disminuida en las concentraciones de eosinófilos y linfocitos en la exacerbación aguda grave del asma en comparación con la exacerbación aguda leve del asma.*

Conclusión: *La concentración de eosinófilos y linfocitos se asoció con la gravedad de la exacerbación aguda del asma.*

Palabras clave: *Asma, exacerbación aguda, eosinófilos, linfocitos.*

INTRODUCTION

Asthma is a chronic inflammatory process of the respiratory tract that involves many cells and their elements. This chronic inflammatory process causes the respiratory tract to become hyperresponsive, thereby facilitating bronchoconstriction, edema, and glandular hypersecretion, which results in restriction of airflow in the respiratory tract and is reversible (1-3). Asthma exacerbations are episodes characterized by a progressive increase in symptoms of shortness of breath, coughing, wheezing, chest tightness, and a progressive decrease in lung function, indicating a change from the patient's normal status sufficient to require a change in (1,4). According to data from GINA (2011), asthma is a heterogeneous disease. It is estimated that around 300 million people worldwide have asthma, and in 2025, it is estimated that the number of asthma patients will increase to 400 million (5,6). Risk factors for asthma that often cause the appearance of asthma symptoms according to their intensity including changes in temperature related to geographic conditions, allergens, physical activity, cigarette smoke, excessive emotional expression, and air pollution (7). As similar to other infections such as *Helicobacter pylor* (8), asthma is also associated with the environmental factors.

Eosinophil cells are a type of leukocyte cells involved in various disease pathogenesis (9). Eosinophils can phagocyte. Eosinophils are active, especially in the late stages of inflammation, when antigen-antibody complexes are formed and play an active role in allergic reactions or parasitic infections to increase the value of eosinophils can be used to diagnose or monitor disease. The normal value of eosinophils is 0-6 % (10). Lymphocytes are responsible for the control of the adaptive immune system. Based on their function and surface markers, lymphocytes are divided into two classes, namely B lymphocytes, which play a role in humoral immunity, and T lymphocytes which play a role in cellular immunity (11). The average concentration of lymphocytes in the blood is 15 %-45 % (10).

Asthma symptoms are varied, multifactorial, and potentially associated with inflammation of the bronchi. The primary inflammatory cells that play a role in asthma are eosinophils and mast cells. Besides, neutrophils and T lymphocytes also play a role in the inflammatory process (12). Many eosinophils accumulate in the bronchial mucosa in chronic asthma, excessive secretion of mucus in the airways, and the smooth muscle becomes hypertrophied and hyperactive to various stimuli. Inflammation and tissue damage in asthma, caused by slow-phase reactions (6-24 hours after re-exposure to allergens), wherein the slow-phase reactions are characterized by inflammation and infiltration of many eosinophils, neutrophils, and T cell lymphocytes (13,14).

The pathophysiology of asthma occurs based on the inflammatory process of the airway triggered by T lymphocytes, which is associated with increased production of cytokines by Th2 relative to the production of cytokines by Th1. The Th2 hypothesis in asthma suggests that a shift in the balance of a Th1-to a Th2-type response modulates eosinophilia, IgE production, airway hyperresponsiveness, and chronic inflammation (15). Several other studies have been conducted to determine how eosinophils and lymphocytes relate to asthma, but they have had different results. A study in 2013 stated that

there was an increase in eosinophil concentration as a characteristic feature of inflammation in asthma and an increase in the concentration of T lymphocytes in the mucosal lumen of the respiratory tract (16). However, in another study, it was found that no increase in eosinophil concentration was found in the complete blood count of asthma patients (17). This study aims to determine the relationship between eosinophil and lymphocyte concentrations and the severity of acute asthma exacerbation.

METHODS

The design of this study was quantitative, analyzing with an observational approach with a cross-sectional retrospective method where this design seeks to determine the relationship between eosinophils and lymphocytes with the severity of acute exacerbation of asthma. The population in this study was taken from acute exacerbation of asthma patients who came to the Emergency Room (ER) at Haji General Hospital, Surabaya, from 2017 to 2019. This research was conducted from December 2019 to March 2020. The sampling technique in this study used a simple random sampling technique, which is to take randomly from the population. The criteria used to select the sample were patients who had been diagnosed with asthma, acute exacerbation of asthma patients who came to the emergency room of General Hospital Haji Surabaya for the period 2017-2019, patients were over 15 years old, and had performed a complete blood count. The instrument used in this study used patient medical record data. In this study, samples of patients with acute asthma exacerbation who had their complete blood checked were then seen the eosinophil and lymphocyte concentrations. After visiting the ER, the patient's discharge condition indicates the severity of the patient's acute exacerbation of asthma. Patients with mild exacerbation of asthma are known if the patient's discharge condition is outpatient, while patients with severe exacerbation of asthma are known if the patient's condition is hospitalized. The data obtained from data collection will be processed and analyzed using a computer program, namely the 25th edition of the Statistical Package for the Social Sciences (SPSS). The non-parametric Mann-Whitney test was used for eosinophils because the data were not normally distributed and had different variants. In comparison, lymphocytes used the Independent T-test because the data were normally distributed and had different variants.

RESULTS

Patient characteristics can be determined based on sex, age, discharge condition, and the number of patient visits. Of the 575 patients, 40 patients met the inclusion criteria. Table 1 displays patients with acute asthma exacerbation in the ER at Haji General Hospital, Surabaya, Indonesia, are more dominated by women. Meanwhile, the patient's age was dominated by the 46-65 age group. In addition, the conditions for discharging patients were proportionately proportional to outpatients and inpatients.

Table 1

Acute exacerbation of asthma patient characteristics in the emergency room of Haji General Hospital, Surabaya, for the 2017-2019 Period

Characteristics	Total	Percentage
Sex		
Male	17	42.5
Female	23	57.5
Age		
15 - 25 years	3	7.5
26 - 45 years	11	27.5
46 - 65 years	16	40.0
>65 years	10	25.0
Returning Conditions		
Outpatient	20	50.0
Inpatients	20	50.0

The statistical analysis shows significant differences in eosinophil (p= 0.003) and lymphocyte (p= 0.000) concentration between mild acute asthma exacerbation and severe acute asthma exacerbation. Figure 1 shows differences in eosinophil and lymphocyte concentrations in two groups of different degrees of asthma

severity, including the mild and severe groups. The mean data of eosinophil concentration in patients with mild acute asthma exacerbation was 2.36 %. There was a decrease in severe acute asthma exacerbation with an average eosinophil concentration of 0.305 %. Meanwhile, the mean data of lymphocyte concentration in patients with mild acute asthma exacerbation was 17.19 %. There was a decrease in severe acute asthma exacerbation with an average lymphocyte concentration of 5.425 %.

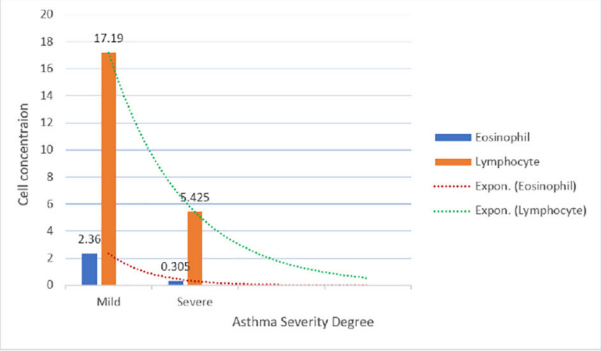

Figure 1. Relationship between the concentration of inflammatory cells and the severity of acute asthma exacerbation.

DISCUSSION

There was a significant difference in the mean values of eosinophil and lymphocyte concentrations with mild acute asthma exacerbation and severe acute asthma exacerbation. The eosinophil concentration in this study tended to decrease with increasing asthma severity. The average eosinophil concentration in mild acute asthma exacerbation was 2.36 %, with the highest value of eosinophil concentration in mild acute asthma exacerbation patients of 10.1 %, indicating the occurrence of eosinophilia process or an increase in eosinophil concentration from the normal range of around 0 %-6 % (10). This is consistent with the theory that a slow-phase reaction causes inflammation and tissue damage in asthma (6-24 hours after re-exposure to an allergen), wherein the slow-phase reaction is characterized by inflammation and infiltration of many eosinophils that accumulate in the bronchial mucosa (13).

In patients with severe acute asthma exacerbation, the mean eosinophil concentration was 0.305 %, with the highest value of eosinophil concentration in severe acute asthma exacerbation patients of 1.2 %. Although the concept of inflammatory eosinophils has long been considered a cause of asthma, there is now a new theory that says that eosinophils' role will be reduced in severe asthma, neutrophils will have a more significant role in respiratory damage in severe asthma (16). Drugs that suppress airway eosinophils, including corticosteroids, anti-IgE, and anti-IL-5, are generally effective in reducing the rate of exacerbation of asthma (12). Furthermore, it can be estimated that the results of eosinophil concentration in patients with severe acute exacerbation of asthma at Haji General Hospital, Surabaya, Indonesia, did not experience an increase in the concentration value because the patients had received previous corticosteroid therapy which had the effect of suppressing airway eosinophils.

The lymphocyte concentration in this study also tended to decrease with increasing asthma severity. The average lymphocyte concentration in mild acute asthma exacerbation was 17.19 %, with the highest value of eosinophil concentration in mild acute asthma exacerbation patients of 42.5 %, which indicates that no patient experienced an increase in lymphocyte concentration from its normal range, namely around 15-45 % (10). It is estimated that the cause of lymphocyte concentration in mild acute asthma exacerbation tends to show normal results because lymphocyte cells arise in slow phase asthma reactions. The slow-phase asthma reaction occurs between 6-9 hours after allergen provocation and involves the recruitment and activation of eosinophils, CD4 + T cells, neutrophils and macrophages. In patients with severe acute asthma exacerbation, the mean lymphocyte concentration was 5.425 % with the highest value of lymphocyte concentration in severe acute asthma exacerbation patients of 11.4 %. The decrease in lymphocyte concentration is due to the administration of corticosteroid therapy in patients with severe acute asthma exacerbation (18). Corticosteroids are effective drugs in inflammation because they cytokines production from both mast cells and

lymphocytes (19). Also, the increasing severity of asthma decreased the patient's lymphocyte concentration because the patient with severe acute exacerbation of asthma at Haji General Hospital, Surabaya, Indonesia, had received corticosteroid therapy treatment. So that when the patient performs a complete blood test, the lymphocyte concentration results obtained will decrease.

The patients with acute exacerbation of asthma are more dominated by women. After puberty, the prevalence of asthma increases at risk in women, with the highest incidence experienced by women with a history of early menarche and multiple pregnancies. This is thought to be due to sex hormonal factors in women (20). The condition of discharge of the patients was proportionally proportional to outpatients and inpatients (21). Patients with mild attacks may be discharged immediately if the asthma symptoms have been relieved and show a positive response by giving nebulization 1x and the symptoms have disappeared. While for patients with severe attacks, if the patient has been nebulized three times, but the response is still inadequate and the symptoms do not disappear, the patient should be hospitalized (22).

CONCLUSION

There was a significant difference in the concentration of eosinophils and lymphocytes with the severity of acute asthma exacerbation, both mild and severe. The concentration of eosinophils and lymphocytes tends to decrease with increasing severity of acute exacerbation of asthma.

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The effect of smoking degree on the incidents of cataracts

Efecto del grado de fumar sobre los incidentes de cataratas

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SUMMARY

Introduction: *A cataract is a condition of the eye lens experiencing turbidity. It is the highest cause of blindness in the world. Smoking is one of the risk factors for cataracts. According to the Brinkman index, the degree of smoking is a multiplication between smoking time and the number of cigarettes consumed in a day. This study aims to analyze the influence of smoking degree on cataracts.*
Methods: *This study employed a cross-sectional research design. The respondents were taken with a consecutive sampling method on 96 cataract patients from December 2019 to January 2020.*
Results: *According to the Brinkman index, most respondents of the study aged 40-59 years were classified into the heavy smoking degree. Most respondents aged ≥ 60 years were classified into mild smoking degrees according to the Brinkman index. Chi-square test results showed a significant difference between heavy smoking and not smoking on the age at which cataracts are diagnosed (p=0.004). There were no significant differences between patients who did not smoke and patients who had mild to moderate degrees of smoking to the age of cataract patients (p=0.085, p=1, respectively). The Spearman test analyzed the correlation between the smoking degree and the age at which cataracts were diagnosed obtained a value of -0.380.*
Conclusion: *There is a significant relationship between smoking degree with the cataract incident on the age at which cataracts are diagnosed.*

Keywords: *Smoking degree, cataract, the Brinkman index.*

RESUMEN

Introducción: *Una catarata es una condición en la que el cristalino del ojo experimenta turbidez. Es la mayor causa de ceguera en el mundo. Fumar es uno de los factores de riesgo de cataratas. Según el índice de Brinkman, el grado de tabaquismo es una multiplicación entre el tiempo que se fuma y la cantidad de cigarrillos consumidos en un día. Este estudio tiene como objetivo analizar la influencia del grado de tabaquismo en las cataratas.*

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Métodos: *Este estudio empleó un diseño de investigación transversal. Los encuestados se tomaron con un método de muestreo consecutivo en 96 pacientes con cataratas desde diciembre de 2019 hasta enero de 2020.*
Resultados: *Según el índice de Brinkman, la mayoría de los encuestados del estudio con edades comprendidas entre los 40 y los 59 años se clasificaron en el grado de tabaquismo intenso. La mayoría de los encuestados de edad ≥ 60 años se clasificaron en grados de tabaquismo leve según el índice de Brinkman. Los resultados de la prueba de Chi-cuadrado mostraron una diferencia significativa entre fumar mucho y no fumar en la edad a la que se diagnostican las cataratas (p=0,004). No hubo diferencias significativas entre los pacientes que no fumaban y los pacientes que tenían grados de tabaquismo de leve a moderado hasta la edad de los pacientes con cataratas (p=0,085, p=1, respectivamente). La prueba de Spearman analizó la correlación entre el grado de tabaquismo y la edad a la que se diagnosticaron cataratas obtuvo un valor de -0,380.*
Conclusión: *Existe una relación significativa entre el grado de tabaquismo y el incidente de cataratas y la edad a la que se diagnostican las cataratas.*

Palabras clave: *Grado de tabaquismo, catarata, índice de Brinkman.*

INTRODUCTION

The eyes have the responsibility to visual and sight, which can be damaged (1). A cataract is one of the conditions where the eye's lens becomes cloudy due to the denaturation of protein in the lens, hydration (addition of fluid) to the lens, or both. Cataracts are characterized by gradual clouding of the lens, which eventually leads to total blindness. Cataracts are the leading cause of blindness in Indonesia (0.78 %) and worldwide (2). Cataract surgery is the most commonly performed operation to treat visual disorders (3-5). However, it has an expensive charge, and most people with cataracts in Indonesia have not yet got surgery due to several factors (6-8). One of the factors cataract patients did not undergo surgery is the attitude that had a dominant influence on the intention to undergo cataract surgery (9). The estimated incidence of cataracts is 0.1 % every year, or among 1 000 people, there is a new cataract sufferer every year. The Indonesian also tends to suffer cataracts 15 years earlier than the population in subtropical areas (10,11).

The pathogenesis of cataracts is not fully understood. However, in a cataract patient's lens, there are protein aggregates that scatter the light beam. A change in protein structure reduces the lens's transparency and induces discoloration of the lens. Additional findings may include vesicles between the lens fibers or epithelial cell migration and abnormal enlargement of epithelial cells. Several factors are thought to play a role in forming cataracts, including oxidative damage (from free radical processes), ultraviolet light, and malnutrition. Until now, no treatment has been found that can slow or reverse the chemical changes that underlie cataract formation (12). The risk factors for cataracts consist of protective, environmental, and individual factors. Protective factors include the use of aspirin and hormone therapy in women. Environmental factors consist of smoking habits, ultraviolet exposure, education level, socioeconomic status, hypertension, diabetes mellitus, steroids, and drugs for gout. Individual factors include gender, age, genetic factors, and race (13).

The smoking habit is an avoidable risk factor. The negative impacts of smoking on health are always listed on cigarette packages, but Indonesians do not care about it. The number of smokers in Indonesia is increasing every year. The number of smokers in Indonesia is even in the third position in the world after China and India (14). Cigarettes are processed tobacco wrapped in cigars or other forms produced by the *Nicotiana tabacum*, *Nicotiana rustica*, and other species or their synthesis containing nicotine and tar with or without additives (15). In tobacco use, there are no established safe thresholds that can be applied in low exposure.

The cigarette smoke component inhaled by smokers consists of part gas (85 %) and part gas (15 %). Cigarettes contain approximately 4 000 types of chemicals, with 60 types of carcinogens (which can cause cancer) (16). The ingredients of cigarettes that can affect the lens are nitric oxide and superoxide anions. These substances cause oxidative stress in the lens and cause the formation of malondialdehyde through lipid peroxidation. Malondialdehyde will form a cross-link between the protein and the lipid membrane, resulting in lens turbidity (cataract) through crystalline

aggregation and the inactivation of antioxidant enzymes in the lens (17).

According to the Brinkman index, the degree of smoking is the result of multiplying the length of smoking by the average number of cigarettes consumed per day. If the result is less than 200, it is called a mild smoker, if the result is between 200-599, it is said to be a moderate smoker, and if the result is more than 600, it is said to be a heavy smoker. The more cigarettes consumed, the longer the smoking, the heavier the smoking degree (15). Smoking as a lifestyle is now starting used in adolescence and even in children. Therefore, this study aims to see the effect of smoking on the incidence of cataracts at a Private Hospital in East Java, Indonesia.

METHODS

This study used a cross-sectional study design. This study's population was cataract patients registered at a Private Hospital in East Java, Indonesia. The subjects of this study were taken by consecutive sampling method with criteria defined in 96 cataract patients. The study was conducted from December 2019 to January 2020. The sample criteria used were cataract patients who were over 40 years old and did not have a history of congenital cataracts, juvenile cataracts, glaucoma, diabetic cataracts, traumatic cataracts, and inflammatory eye disease. The research sample will be selected based on medical records. The selected sample will receive a questionnaire asking for identity, history, education level, and smoking history. The results of the observations were then processed using the chi-square and spearman tests using the SPSS Statistics 25 application. The chi-square test was used to find significant differences between smoking degrees and the age at which cataracts were diagnosed. The Spearman test was performed to determine the effect of smoking on cataracts.

RESULTS

Table 1 describes the respondents' characteristics that most of the cataract patients are male and aged ≥60 years. Most of the respondents have an elementary education background or equivalent, and the majority work as farmers.

Table 1

Respondents' Characteristics

Variable	Frequency	Percentage
Sex		
Male	78	81.3
Female	18	18.7
Age (Year)		
40-59	42	43.8
≥60	54	56.2
Educational Stage		
Do not go to school	22	22.9
Elementary School	43	44.8
Junior High School	7	7.3
Senior High School	15	15.6
College	9	9.4
Occupation		
Housekeeping	7	7.3
General Employees	24	25.0
Government Employees	6	6.3
Farmers	34	35.4
Trader	4	4.2
Teacher	4	4.2
Retired	2	2.1
Enterpreneur	12	12.5
Another Job	2	2.1
Freelance	1	1.0
Total	96	100.0

The age category on cataract patients was classified as 40-59 years old and ≥60 years. The Chi-square test obtained no significant difference between non-smoking and mild smoking on the age at which cataracts were diagnosed (p=0.085). There was also no difference between non-smoking and moderate smoking at the age at which cataracts were diagnosed (p=1). However, there was a difference between not smoking and heavy smoking at the age of cataract diagnosis (p=0.004). Table 2 shows that the Spearman method's test results were -0.380 indicating a sufficient correlation between the smoking degree and the age at which cataracts were diagnosed.

Table 2

Effect of smoking degree on cataract incidence

Age	Smoking Degree				Total
	Non-Smoking	Mild	Moderate	Heavy	
40-59 Years	9	5	5	23	42
≥60 Years	14	28	7	5	54
Total	23	33	12	28	96

The result using Spearman method = -0.380

DISCUSSION

This study found that most respondents with a heavy smoking degree suffered from cataracts at the age of 40-59 years. Most cataract patients diagnosed at ≥60 years old had mild smoking degrees and had no smoke history. The number of cataract sufferers with the degree of mild smoking was twice as high compared with the number of cataract patients who do not smoke at ≥60 years old. There is a significant difference between cataract patients who do not smoke and the heavy smoking degree to the incidence of cataracts. The lens can experience the turbidity of the reactive oxygen species (ROS) contained in cigarettes (17). ROS is a substance that can cause membrane lipid peroxidation and form malondialdehyde. Malondialdehyde will destroy cells by forming cross-links between proteins and lipid membranes. The lens has enzymes that function to protect against free radicals, including catalase and glutathione peroxidase. However, polymerization and cross-linking of these proteins lead to the inactivation of lens protective enzymes and crystalline aggregation (17). Also, there was an influence between smoking habits and the incidence of cataracts. Respondents with a history of smoking had a 5.182 times higher risk of developing cataracts than non-smokers (18).

The heavier the degree of smoking, the higher the risk of cataracts, in line with a previous study conducted in Kendari, Indonesia. Based on the Brinkman index, which is the result of multiplying the length of smoking and the number of cigarettes smoked in a day, it can be seen that the heavier the degree of smoking, the higher cataracts that occur (19). The previous report also shows the relationship between smoking and the incidence of senile cataracts in the Eye Clinic of Bakinang Hospital, Indonesia. Smoking history had a 7.5 times greater chance of experiencing cataracts in smoking respondents compared to non-smoking respondents. Smoking can induce oxidative stress and a decrease in ascorbate, carotenoids, and antioxidants that, over time it can cause lens turbidity (20).

Smoking can cause the build-up of chromophores. Chromophores can cause the lens to turn yellow. Cigarettes also contain cyanates which can cause carbamylation and denaturation of lens proteins. A study indicates that respondents who have a history of smoking have a high risk of developing cataracts (OR= 2.771) (21). Another report states that respondents who have a smoking habit have a 2.934 times higher risk of being diagnosed with cataracts. Smoking can damage cell membranes and lens fibers (22).

There are limitations to the study. The subjects in this study were cataract patients registered in December 2019-January 2020 so that the data obtained can be called the latest data. However, the instrument in this study was a questionnaire without periodic observation. In this study, other variables may influence the incidence of cataracts. Further research is needed to see the relationship between smoking degrees and the cataract stage. The time of initial diagnosis of cataracts to the degree of smoking can also be investigated further.

CONCLUSION

Most respondents with a heavy smoking degree suffered from cataracts at the age of 40-59 years. At the same time, most cataract patients diagnosed at ≥60 years old had mild smoking degrees and had no smoke history. The smoking degree had a significant appearance in cataract incidents on the age at cataracts diagnosed at a Private Hospital in East Java, Indonesia.

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Immunoglobulin-E and Thyroid-Stimulating Hormone Receptor Antibody in Graves' disease with Atopy

Inmunoglobulina E y el receptor del anticuerpo de la hormona estimulante de la tiroides en la enfermedad de Graves con atopia

Rio Wironegoro[1*•], Ari Baskoro[2**], Chairul Effendi[3**], Agung Pranoto[4*]

SUMMARY

Background: *Graves' disease is known to have a high recurrence rate with recent evidence linked pollen allergy as one of the factors that might induce relapse in Graves' disease. Therefore, it was argued that IgE might play a role in inducing relapse of Graves' Disease. This study aims to investigate the correlation between IgE and Thyroid-Stimulating Hormone Receptor Antibody (TRAb) in Graves' disease respondents with a history of atopy.*
Methods: *A cross-sectional study was conducted in 2012. Blood samples were collected using a 5 mL sterile syringe, put on EDTA tubes, and analyzed for Routine Blood Count, IgE level, and TRAb level. Stool examination and skin prick test data were also collected from the respondents to determine the history of atopy.*
Results: *A total of 131 respondents participated in this study, consisting of 28 males (20.6 %) and 103 females (79.4 %). In the group with a history of atopy, the average atopy duration was 26.5 years, and the most common types of atopy were allergic rhinitis (42.6 %), food allergy (32.3 %), asthma (16.1 %), and drug allergy (8.8 %). IgE level and TRAb level among respondents with a history of atopy were significantly higher than those without a history of atopy (407 vs. 23.9 for IgE; 9.2 vs. 1.4 for TRAb). We found a positive correlation between IgE level and TRAb level among respondents with a history of atopy (r=0.580; p<0.0001).*
Conclusion: This study found a significant correlation between IgE level and TRAb level among Graves' disease respondents with atopy history.

Keywords: *Atopy, graves' disease, immunoglobulin-E, thyroid-stimulating hormone receptor antibodies.*

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RESUMEN

Antecedentes: *Se sabe que la enfermedad de Graves tiene una alta tasa de recurrencia con evidencia reciente que relaciona la alergia al polen como uno de los factores que podrían inducir una recaída en la enfermedad de Graves. Por lo tanto, se argumentó que la IgE podría desempeñar un papel en la inducción de la recaída de la enfermedad de Graves. Este estudio tiene como objetivo investigar la correlación entre la IgE y el receptor del anticuerpo de la hormona estimulante de la tiroides (TRAb) en los encuestados con enfermedad de Graves con antecedentes de atopia.*
Métodos: *Se realizó un estudio transversal en 2012. Se recolectaron muestras de sangre usando una jeringa estéril de 5 mL, se colocaron en tubos con EDTA y se analizaron para el recuento sanguíneo de rutina, el nivel de IgE y el nivel de TRAb. También se recopilaron datos de exámenes de heces y pruebas cutáneas de los encuestados para determinar el historial de atopia.*
Resultados: *Un total de 131 encuestados participaron en este estudio, compuesto por 28 hombres (20,6 %) y 103 mujeres (79,4 %). En el grupo con antecedentes de atopia, la duración media de la atopia fue de 26,5 años, y los tipos más frecuentes de atopia fueron rinitis alérgica (42,6 %), alergia alimentaria (32,3 %), asma (16,1 %) y alergia a fármacos (8,8 %). El nivel de IgE y el nivel de TRAb entre los encuestados con antecedentes de atopía fueron significativamente más altos que aquellos sin antecedentes de atopia (407 frente a 23,9 para IgE; 9,2 frente a 1,4 para TRAb). Sse encontró una correlación positiva entre el nivel de IgE y el nivel de TRAb entre los encuestados con antecedentes de atopia (r= 0,580; p<0,0001).*
Conclusión: *Este estudio encontró una correlación significativa entre el nivel de IgE y el nivel de TRAb entre los encuestados con enfermedad de Graves con antecedentes de atopia.*

Palabras clave: **A***topia, enfermedad de Graves, inmunoglobulina E, anticuerpos receptores de la hormona estimulante del tiroides.*

INTRODUCTION

Graves' disease is an autoimmune disorder characterized by the production of Thyroid-Stimulating Hormone Receptor Antibody (TRAb) which activates and causes excessive thyroid hormone synthesis and release. Graves' disease is the most common cause of hyperthyroidism, a typical presentation among females aged 40 – 60 years (1). Although the prevalence among general populations was around 1 % - 1.5 %, Graves' disease is known to have a high recurrence rate. One study described a recurrence rate of 50 % during the 4-year follow-up course among patients with Graves' disease (2).

The etiology of recurrence in Graves' disease is still unknown, recent evidence linked pollen allergy as one of the factors that might induce relapse in Graves' disease (3). Pollen allergy is one of the diseases related to Immunoglobulin-E (IgE) synthesis. It was argued that IgE might play a role in inducing relapse of Graves' Disease. IgE levels were elevated in 29 % of those with Graves' disease.

Although the incidence of increased IgE levels was smaller than in patients with bronchial asthma (63 %) or pollen allergy (40 %), the mean value of IgE increase in subjects suffering from Graves' disease was equal in subjects suffering from bronchial asthma, and even greater when compared to people with pollen allergy. Therefore, it appears that elevated IgE levels are associated with Graves 'autoimmune disease (3).

Previous studies have found that 30 %-40 % of people with Graves' disease have elevated levels of immunoglobulin-E (IgE). Some evidence also suggests a link between autoimmune thyroid disease and allergic responses. Several findings that might support this argument are 1) IgE was found in thyroid tissue and ocular muscle in subjects with Graves' disease, 2) Recurrence of Graves' disease was linked to allergic rhinitis, 3) Several studies reported an IgE class of thyroid peroxidases autoantibodies among subjects with Hashimoto Thyroiditis and Graves' disease, and 4) A significant increase of IgE level in 29 % - 40 % subjects with Graves' disease. Studies also revealed that the remission rate in patients with Graves' disease associated with an increase in IgE levels is lower than in patients with Graves' disease with normal IgE levels (3-5).

However, no study had been conducted to confirm whether IgE is correlated directly with Graves' disease progression. This study aims to compare the IgE level and TRAb level among Graves' disease subjects based on atopy status.

METHODS

Study Design

This was a cross-sectional study conducted from April to August 2012 at the Endocrinology outpatient clinic, Dr. Soetomo General Hospital, Surabaya, Indonesia. Subjects were Graves' disease patients aged 18 years and above that have fulfilled the diagnostic criteria and received Propylthiouracil (PTU) treatment for at least eight weeks. Using sample size calculation, we obtained the minimum requirement was 38 responses (6). Consecutive sampling was conducted until the minimum number is fulfilled. This study followed the principles of Helsinki's Declaration and also received permission from Dr. Soetomo General Hospital Ethical Committee before it began (ethical clearance o.0050/LOE/301.4.2/VI/2012). All respondents had given their informed consent before their inclusion in the study. Details that might disclose the identity of the respondents were omitted.

Data Collection

We obtained respondents through interviews using a structured questionnaire which consisted of sociodemographic data, disease condition, treatment data, and allergy history. The physical examination was then conducted to obtain information on respondents' vital signs (blood pressure, heart rate, respiration rate, and body temperature) using standardized protocols.

Blood samples were collected using a 5 mL sterile syringe, put on EDTA tubes, and analyzed for Routine Blood Count, IgE level, and TRAb level. Stool examination and skin prick test data were also collected from the respondents to determine the history of atopy.

Data Analysis

Acquired data were compiled and analyzed using IBM SPSS for Windows ver. 20.0. Demographical data were presented in frequency tables, while IgE and TRAb level was expressed as mean ± standard deviation. Correlation between IgE and TRAb level in respondents with atopy were analyzed using Spearman rank-order.

RESULTS

A total of 131 respondents were included in this study, consisting of 28 males (20.6 %) and 103 females (79.4 %). Respondents were then further categorized based on a history of atopy; age distribution was shown in Table 1. In the group with a history of atopy, the average atopy duration was 26.5 years, and the most common types of atopy were allergic rhinitis (42.6 %), food allergy (32.3 %), asthma (16.1 %), and drug allergy (8.8 %).

Table 1.

Respondent Age Distribution

	Without Atopy n = 63	With Atopy n = 68
Mean age (years)	42.2	45.4
Age group		
< 20 years	0 (0)	1 (1.5)
20 – 29 years	8 (12.6)	6 (8.8)
30 – 39 years	18 (28.5)	13 (19.1)
40 – 49 years	19 (30.1)	16 (23.5)
50 – 59 years	14 (22.2)	23 (33.8)
60 – 69 years	4 (6.6)	8 (11.8)
> 69 years	0 (0)	1 (1.5)

We analyze the laboratory data collected from the respondent. We found that the mean total IgE level in respondents with and without a history of atopy consecutively 407 IU/mL and 23.9 IU/mL. Total TRAb level in respondents with and without a history of atopy consecutively 9.2 IU/mL and 1.4 IU/mL. It was found that both IgE level and total TRAb level in respondents with a history of atopy are higher than respondents without a history of atopy.

We further analyze the correlation between IgE level and TRAb level in respondents with a history of atopy. It was found that TRAb level was positively correlated with IgE level ($r=0.580$; $p<0.0001$).

DISCUSSION

Graves' disease is a polygenic disease that occurred due to interaction between genetic susceptibility, environmental factors, and endogenous factors (7). Interaction between these factors remained unclear and researches are needed to shed some light on this topic. This study agreed with previous studies that showed Graves' disease affects females 4 – 5 times more likely than males, with the age group of 30 – 50 years old being the most susceptible to this disease (8). This study found that 51.9 % of respondents with Graves' disease had a history of atopy. This finding is in accordance with a previous study that reported 30 % - 50 % of respondents with Graves' disease have at least one type of atopy (7-9). Regarding the IgE level among respondents with and without a history of atopy, this study was in accordance with a previous study (9), which shows that IgE level in subjects with a history of atopy was significantly higher than subjects without a history of atopy. It was argued that respondents with a history of atopy would synthesize a higher level of IgE as a response toward environmental allergens. In comparison, those without a history of atopy will synthesize other antibody types such as IgG and IgM in a higher level while only a small number of IgE (10). This study found that the TRAb level in respondents with a history of atopy was significantly higher than those without a history of atopy.

In Sato's study, Graves' disease subjects with above average IgE levels will have significantly higher TRAb levels than those with normal IgE levels. Sato's study also revealed that before receiving methimazole therapy, TRAb levels in Graves 'disease patients who experience elevated IgE levels are higher than those with Graves' disease patients with normal IgE levels. However, while receiving methimazole therapy, even though both groups experienced a decrease in TRAb levels, the decrease was significantly developed in the group of Graves' disease patients with normal IgE levels. Another previous study also showed a positive correlation between IgE level and TRAb level in Graves' disease subjects with a positive history of asthma and allergic rhinitis (11). We further explore the correlation between IgE level and TRAb level in this study. Using the Spearman-rank order test, we found a positive correlation between IgE level and TRAb level among respondents with atopy history.

This study has several limitations. Firstly, this study was only conducted in a single center, which may not represent Indonesia or Surabaya population. Second, there was a limited amount of funds available for this study, which caused fewer parameters to be examined in this study. Therefore, the authors recommend further study in Graves' disease subject with a history of atopy to obtain an optimal treatment result and prevent recurrence in the future.

CONCLUSION

We found that IgE level and TRAb level in Graves' disease respondents with a history of atopy were significantly higher than those without a history of atopy. We also found a positive correlation between IgE level and TRAb level in Graves' disease respondents with a history of atopy. The result of this study may be used to investigate further the correlation between Graves' disease and history of atopy.

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Maternal age and parity associated with low birth weight infants

Edad materna y parto asociados con infantes con bajo peso al nacer

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SUMMARY

Introduction: *Low birth weight (LBW) infants indicate infant morbidity and infant mortality rates. In Indonesia, the infant mortality rate is still very high, with 32 deaths per 1 000 live births. The purpose of this study is to prove a relationship between maternal age and parity with LBW infants.*
Methods: *This study used an observational cross-section study design. The sample selection used total sampling with a sample of 117 samples. The sample was collected from the medical record of Muhammadiyah Hospital of Surabaya for 12 months in 2018.*
Results: *There were 74 mothers (63.2 %) of at-risk age, and 110 mothers (94 %) had risk parity. There was a significant effect of maternal age on infant birth weight (p=0.000). Mothers with a risk age increased the tendency to give birth to LBW infants by 52.720 times. There was a significant effect of maternal parity on infant birth weight (p=0.014). Mothers with parity at risk increased the likelihood of giving birth to infants with LBW by 36.856 times. The formula predicts the occurrence of LBW is equal with -11.126+3.965*Age+3.607*Parity.*
Conclusion: *Maternal age and parity were associated with LBW infants.*

Keywords: *Low birth weight, age, parity, maternal.*

RESUMEN

Introducción: *Los lactantes con bajo peso al nacer (BPN) indican tasas de morbilidad y mortalidad infantil. En Indonesia, la tasa de mortalidad infantil sigue siendo muy alta, con 32 muertes por cada 1 000 nacidos vivos. El propósito de este estudio es probar una relación entre la edad materna y la paridad con los bebés de bajo peso al nacer.*

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Métodos: *Este estudio utilizó un diseño de estudio observacional de corte transversal. La selección de la muestra utilizó un muestreo total con una muestra de 117 muestras. La muestra se tomó del expediente médico del Hospital Muhammadiyah de Surabaya durante 12 meses en 2018.*
Resultados: *Había 74 madres (63,2 %) en edad de riesgo y 110 madres (94 %) tenían paridad de riesgo. Hubo un efecto significativo de la edad materna sobre el peso al nacer del bebé (p=0,000). Las madres con edad de riesgo incrementaron la tendencia a dar a luz a bebés de bajo peso al nacer en 52 720 veces. Hubo un efecto significativo de la paridad materna sobre el peso al nacer del bebé (p=0,014). Las madres con paridad en riesgo aumentaron la probabilidad de dar a luz a bebés con BPN en 36 856 veces. La fórmula predice que la ocurrencia de BPN es igual a -11 126 + 3 965 * Edad + 3 607 * Paridad.*
Conclusión: *La edad materna y la paridad se asociaron con los lactantes de bajo peso al nacer.*

Palabras clave: *Bajo peso al nacer, edad, paridad, materno.*

INTRODUCTION

The infant mortality rate in Indonesia is still very high compared to other developing countries based on the 2013 Central Bureau of Statistics. Infant Mortality Rate in Indonesia reached 32 deaths per 1 000 live births in 2013, making Indonesia one of the countries with the highest IMR in ASEAN (1). One of the causes of infant mortality in Indonesia is low birth weight (LBW) infants of 38.85 %. The following year the Sustainable Development Goals (SDGs) were used until 2030, namely by reducing the maternal and infant mortality rates by 12 per 1 000 live births (2). The purpose of the SDGs is implemented in East Java Province, Indonesia, by implementing 4 per 1 000 live births to improve health even better and reflect superior health (1).

LBW are newborns born weighing <2,500 grams without assessing gestation (3). LBW infants are very susceptible to illness (4). In 1961 by the World Health Organization (WHO), all infants born with fewer than 2,500 grams were called LBW Infants. Many still think that LBW only occurs in premature infants or infants who are not full-term. However, LBW can not only occur in premature infants. It can also occur in term infants who experience a process of inhibition in their growth during pregnancy (1). LBW is caused by multifactorial factors such as maternal factors, placental factors, fetal factors, and environmental factors (5). LBW is mostly found because the mother's age is not ready to conceive during pregnancy (6,7). Maternal age at pregnancy is also related to a woman's age at marriage. Women who marry at an early age have the opportunity to get pregnant at a young age, too (8). Previous studies also report that LBW may be caused by malaria during pregnancy (9,10).

The clinical manifestations of LBW can be divided based on prematurity and immaturity. Clinical manifestations of prematurity are: birth weight <2,500 grams, body length <45 cm, chest circumference <30 cm, and head circumference <33 cm. The period of gestation is less than 37 weeks. It is thin and shiny skin, less subcutaneous fat, very soft ear cartilage, lots of lanugo, especially in the dorsal region, the blood vessels of the skin are still visible, and the nipples have not been properly developed. In the labia majora of female sex infants, the labia minora cannot close. In comparison, the testes have not decreased in male infants. Other manifestations are lack of movement, weakness, and muscle tone are hypotonic, weeping and sluggish, and breathing is not normal, repeated apnea attacks, neck tonic reflexes are still weak, suck and swallow reflexes have not reached perfect levels (11).

Apart from prematurity, there is also immaturity. The clinical manifestations of immaturity are as follows: pale skin, such as blemishes, meconium or dry, wrinkled, and thin stools, thin or absent vernix caseosa, thin fatty tissue under the skin, the baby looks fast, active and healthy, the umbilical cord is slightly greenish-yellow (11). Other factors can also be obtained from the maternal parity factor that occurs during childbirth. Besides, mothers must also pay more attention to adequate nutrition to meet the needs of mothers and infants who can be born with sufficient weight (6). Based on this background, this study aims to determine the relationship between maternal age and parity with LBW infants.

METHODS

An observational cross-sectional approach was used in this analysis. This research used the information to test a correlation study's design between two variables from a sample group. The independent variable was LBW infant, and the dependent variable was the age of the baby's mother and their parity. The research instrument is secondary data obtained from mothers who give birth and infants born in Muhammadiyah Surabaya Hospital, Indonesia, as long as 12 months of the year 2018. The data collected with consecutive criteria of as many as 117 samples. The inclusion criteria were complete medical records, pregnancy over 20 weeks, normal parturient, the parturient distance over two years, no chronic illness, no history of pre-eclampsia and pre-during-postpartum bleeding, no substance abuse, no smoking, no alcohol use, no history of infection during pregnancy, and regular antenatal care. The exclusion criterion was the cesarean section in a parturient. The data obtained were then processed using the statistical analysis technique of the Chi-Square correlation coefficient test.

RESULTS

The total sample of LBW infants whose mothers had normal parturient in the medical record was 117 samples within a year. Table 1 shows that the majority of mother in this study was at risk age. Most infants' weight was included in the LBW group. Table 1 shows that there is a respondent with a risk age, namely those aged <20 or >35 years. The respondents who were not at risk were in the 20-35 age group.

Furthermore, it can be seen that there was a respondent with risk parity, namely parity 1 or ≥4. The number of respondents with no risk parity, 2-3, was 6.0 %. Also, it can be seen that the number of respondents with LBW infants, namely <2,500 grams, was 73.5 %. The number of respondents with average baby weight, average birth weight (ABW), namely ≥2,500 grams, was 26.5 %. The minimum mother's age was 18 years, and the maximum was 44 years. The mother's minimum parity was 0, the maximum was 5, and the average was 1.04. For infants, the minimum birth weight was 2,200 grams; 2,500 grams was the maximum.

Table 1

Distribution of Respondents

Variable	Description	N (%)	Mean	SD	Min	Max
Mother's age (years)	At risk (<20 & >35)	74 (63.2)	31.4	7.8	18	44
	Not at risk (20-35)	43 (36.8)				
Mother's parity	At-risk (1 or ≥ 4)	110 (94)	1.0	1.4	0	5
	Not at risk (2-3)	7 (6)				
Baby Weight	LBW	86 (73.5)	2,407.7	79.0	2,200	2,500
	ABW	31 (26.5)				

LBW: Low birth weight
ABW: average birth weight

Bivariate analysis showed that the mother's age at risk (p=0.000) and mother's parity (p=0.014) were significantly associated with LBW. The result of the correlation of maternal age and parity to LBW infants can be seen in Table 2. It obtained a formula to predict the occurrence of LBW infants. The Nagelkerke R-Square value was 0.568, indicating that the independent variable's ability to explain the dependent variable was 56.8 %. There were 100 % - 56.8 % = 43.2 % other factors outside the model that explained the dependent variable. This test determined each

independent variable's effect (mother's age and parity) on the dependent variable (LBW). Based on the results of the logistic regression test from Table 2, the regression equation obtained is as follows to predict the occurrence of LBW infant: LBW= -11 126+3 965*Age+3 607*Parity.

Table 2

Relationship between maternal age and parity to LBW

	b	Wald	p	OR	95 %	CI
Age	3.965	25.630	0.000	52.720	11.359	244.696
Parity	3.607	9.183	0.002	36.856	3.575	379.923
Constant	-11.126	22.456	0.000	0.000		

Nagelkerke R squere = 56.8%; Hosmer & Lemeshow test = 0.948

DISCUSSION

This study proves that maternal age and maternal parity were associated with LBW. The maternal age had a risk of 52.720 times for the occurrence of LBW. Besides, maternal parity had risks 36.856 times higher of giving birth to an LBW. It is in line with a study in South Korea that found maternal age and parity contribute 79 % of LBW (12). Another study also found that grand multiparous women contribute 3.89 times LBW compared to multiparous women. Nulliparous women 0.23 times compared to multiparous women. Primiparous women contribute 0.22 times compared to multiparous women. Women aged 40 and above contribute 1.96 times compared to women aged 30-34 (13). Our study had different results from this study; contrary, maternal parity had a more significant effect than maternal age. Another study divided the parity into three groups, including grande multiparous, multiparous, and nulliparous (13), while our study only divided into two groups, not at-risk (multiparous, 2-3) and at-risk (nulliparous and grande multiparous, ≥4). In addition, maternal age >35 years also can interfere with circulation in the uterine organs during pregnancy. Circulatory disorders in pregnant women can lead to LBW infants and the occurrence of preeclampsia (14).

Maternal age will influence mothers to give birth to LBW infants. When the mother is <20 years of age, the reproductive organs and physiological functions are not yet optimal; besides, their emotions and psychology are not mature enough to prevent the mother from reacting correctly to her pregnancy during pregnancy (15). Meanwhile, pregnancies above 35 years of age are also not recommended, considering that diseases such as hypertension, benign tumors, and other degenerative diseases often appear (16). The previous report revealed that the age factor affected 1.7 times the occurrence of LBW (17). A study also shows maternal age had a significant effect on the occurrence of LBW (18). The incidence rates of adverse infant outcomes began to increase at the maternal age of 30 years. The maternal age of ≥35 years was associated with significantly increased risks of adverse infant outcomes, including small for gestational age 1.15 times, LBW 1.29 times, and preterm birth 1.17 times (19).

Mothers who have given birth to children more than three times are at risk of giving birth to LBW infants. Other studies show that parity has four times the risk of LBW (17,20). Another report also found that maternal age had a significant effect on LBW occurrence (18). This condition is because the uterus is usually weak due to decreased reproductive organs, so that muscle cells begin to weaken and other body parts have decreased to cause an increase in LBW incident. The results showed that parity is a high-risk factor for LBW, where mothers with parity >3 children will be at risk of giving birth to LBW twice (15).

This study demonstrated that mothers with high parity can influence mothers to give birth to LBW infants because repeated pregnancies will damage the uterine blood vessels' walls. This condition will affect nutrition to the fetus in subsequent pregnancies to cause fetal growth disorders. Who, in turn, will give birth to a baby with LBW. Other factors associated with LBW incidence in newborns are anemia (21), a history of LBW in previous labor, and placenta previa (22).

CONCLUSION

There was a significant effect of maternal age and parity on the birth weight of infants. Mothers with a risk age and parity increased the tendency to give an LBW of their infants by 52.720 and 36.856 times, respectively.

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Conflicts of Interest

The authors declare no conflict of interest.

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Etiological pathogen causes of diarrhea in children

Patógenos etiológicos causantes de diarrea en niños

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SUMMARY

Introduction: *The incidence of diarrhea in early childhood in developing countries has a mortality rate of nearly one million each year. This study aims to determine the pathogens that cause diarrhea in children based on their groups.*
Methods: *Information was obtained using several relevant keywords through search engines or online databases such as PubMed, Google Scholar, and SINTA websites with keywords "etiology", "pathogen", "causes", and "diarrhea in the child". The publication years were 2010 to 2020 with the minimum publication category indexed by Scopus and SINTA 4.*
Results: *There were three groups of pathogens found, including viruses, bacteria, and parasites. The most common type of virus found in 6 articles is Rotavirus. Four articles mention Escherichia coli as the bacterial pathogen in the bacterial group that causes the most diarrhea. In comparison, the most types of parasites found in five journals were Cryptosporidium sp. The age range of children who were more frequently sampled was 0-5 years. Many cases of diarrhea are found at the age of 0-5 years because the immune system in infants and toddlers (under five years old) is still learning to recognize and protect the body from incoming pathogens so that they are more susceptible to infection. Of the 12 research articles identified, Polymerase Chain Reaction was used.*
Conclusion: *The most common type of virus was Rotavirus. In the bacterial group, E. coli is the bacterial pathogen that causes the most diarrhea. In comparison, the most type of parasite found was Cryptosporidium sp.*

Keywords: *Diarrhea, etiology, pathogens.*

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RESUMEN

Introducción: *La incidencia de diarrea en la primera infancia en los países en desarrollo tiene una tasa de mortalidad de casi un millón cada año. Este estudio tiene como objetivo determinar los patógenos que causan diarrea en los niños en función de sus grupos.*
Métodos: *La información se obtuvo utilizando varias palabras clave relevantes a través de motores de búsqueda o bases de datos en línea como PubMed, Google Scholar y sitios web SINTA con las palabras clave "etiología", "patógeno", "causas" y "diarrea en*

el niño". Los años de publicación fueron 2010 a 2020 con la categoría de publicación mínima indexada por Scopus y SINTA 4.
Resultados: *Se encontraron tres grupos de patógenos, incluidos virus, bacterias y parásitos. El tipo de virus más común encontrado en 6 artículos es el rotavirus. Cuatro artículos mencionan a Escherichia coli como el patógeno bacteriano, en el grupo bacteriano, que causa más diarrea. En comparación, la mayoría de los tipos de parásitos encontrados en cinco revistas fueron Cryptosporidium sp. El rango de edad de los niños que fueron muestreados con mayor frecuencia fue de 0 a 5 años. Muchos casos de diarrea se encuentran entre los 0 y los 5 años porque el sistema inmunológico de los bebés y niños pequeños (menores de cinco años) todavía está aprendiendo a reconocer y proteger el cuerpo de los patógenos entrantes para que sean más susceptibles a las infecciones. De los 12 artículos de investigación identificados, se utilizó la reacción en cadena de la polimerasa.*
Conclusión: *El tipo de virus más común fue el rotavirus. En el grupo bacteriano, E. coli es el patógeno bacteriano que causa más diarrea. En comparación, el tipo de parásito más encontrado fue Cryptosporidium sp.*

Palabras clave: *Diarrea, etiología, patógenos.*

INTRODUCTION

The incidence of diarrhea in early childhood in developing countries has a mortality rate of nearly one million each year (1). Diarrhea is one of the significant foodborne in children (2). It is a leading cause of dehydration in infants and children age five, and over mild to moderate diarrhea can result in missed school days and may require treatment by a health care provider. Diarrhea that is more severe and lasts longer will require hospitalization (3-5). Therefore, Mortality Research and Basic Health Research states that diarrhea is still the leading cause of child mortality in Indonesia for years (6).

It is well known that the majority of diarrheal episodes are self-limiting. Although oral rehydration therapy can normally be used to treat dehydrated patients, it would be better if it could also be used to prevent diarrhea in children (3-5). This is due to the results of the 2013 Basic Health Research (Riskesdas) report that diarrhea is still the most common cause of infant mortality in Indonesia, namely 46 %, while the cause of death for children aged 1-4 years is caused by diarrhea as much as 25 % (7). Numerous prevention methods, such as improving water sanitation, implementing basic hygiene practices, and ensuring the hygiene of milk bottle-feeding, are easy to implement (2,8,9). Another study also suggests improving women's empowerment as an important strategy to prevent diarrhea (10).

The etiology of diarrhea is divided into two factors, including infection and non-infection (11). Infectious diarrhea can be caused by viruses, bacteria, parasites, and fungi (12). Infection is depending on the variation of bacterial virulence, host genetics, and/or environmental factors (13). Meanwhile, non-infectious diarrhea is caused by allergies, food intolerance, colitis, celiac disease, and poisoning. Diarrhea caused by infection has more cases and a number of deaths than non-infectious diarrhea. Several laboratory examination methods diagnose pathogens that cause infectious diarrhea, including culture, serological tests, polymerase chain reaction (PCR), and microscopic examination. Several pathogens that infect the digestive system itself can produce toxins, causing inflammation and damage to the mucus and intestinal microvilli. Damage to the intestine itself can be characterized by diarrhea with blood. In the above conditions, if not handled immediately, it is leading to death (14).

Numerous experiments have been performed in countries around the world to assess if one or more pathogens are present in diarrhea stool. Although isolated studies on specific pathogens can yield valuable information, it is difficult to determine the relative importance of different pathogens without considering the entire spectrum of agents. As such, this study aims to collect data on the annual incidence and mortality rates of a number of potential pathogens in this age group.

METHODS

Online databases such as PubMed, Google Scholar, and 6 SINTA was searched using the following several relevant keywords: "Etiology", "Pathogen", "Causes", and "diarrhea in the child" with the publication year of 2010 to 2020, with

the minimum publication category indexed by Scopus and SINTA 4. Analyzing the data was carried out through bibliographic annotation analysis.

The author first reviewed journal titles and abstracts for the suitability of the screening process based on relevant keywords and sort by concurrently identified broad-spectrum pathogens so that it did not include research journals based on specific pathogens. The information cited relates to the study population, study setting, definition of diarrhea, prevalence of each pathogen, and information on diarrhea pathogens required to be included in the literature review. Furthermore, analyzing the data was carried out through annotated bibliography analysis (annotated bibliography). Bibliographic annotation can be concluded as a list of sources used in a study, where each source is given a conclusion related to what is written in it.

RESULTS

The authors list several articles that are used as references for writing literature reviews in the form of Table 1.

Table 1 shows that there are three groups of pathogens found, namely viruses, bacteria, and parasites. The most common type of virus found in six articles was Rotavirus. In the bacterial group, four articles mention *Escherichia coli* as the bacterial pathogen that causes the most diarrhea. While the most types of parasites found in the 5 articles were *Cryptosporidium sp*. The group of fungal pathogens was not found in the 12 articles.

Table 2 shows diarrhea pathogens based on several studies. Of the 12 research articles identified using PCR, six research articles only used PCR to identify viruses, bacteria, and parasites at once. In four research articles, PCR examination was combined with culture examination, and three research articles combined PCR with the serological examination. The classification of pathogens and pathogenesis of pathogens in causing diarrhea varies depending on the species of the pathogen. This literature review realizes that national-level community-based hospital and surveillance reports will enable a country to better understand the level of local disease through pathogens and can serve as a reference for better prevention programs. In addition, the age range of children who were more frequently sampled was 0-5 years. Of the 11 studies, a sample aged 0-5 years was used. Only one study used a sample of 0-17 years old.

DISCUSSION

The most common type of virus found in 6 articles was Rotavirus. Morbidity peaked in 2003, and the virus mostly affects children under the age of three. Rotavirus requires only a small number of infectious virions to cause disease in susceptible hosts. Rotavirus infection will cause malabsorption of carbohydrates and loss of fluid from digestion because the death of enterocyte cells will release the cytoplasm into the intestinal lumen. Also, changes in function in the villi caused by the virus induce an increase in intestinal motility, worsening the situation (15,16).

In the bacterial group, 4 articles mention E. coli as the bacterial pathogen that causes the most diarrhea. The evolution of pathogenic E. coli, which culminated in the development of distinct pathotypes capable of colonizing the gastrointestinal tract, urinary tract, and meninges, demonstrates how genetic strains can adapt to a variety of host environments. The process of evolution has produced highly capable species capable of colonizing, multiplying, and destroying diverse environments. Due to the ability of various *E. coli* virulence factors to affect a broad variety of cellular functions, various toxins, effectors, and cell surface structures have been used to gain a deeper understanding of these fundamental eukaryotic processes (17).

The most type of parasite found in the 5 articles was *Cryptosporidium sp*. Cryptosporidium can survive in the environment as oocysts containing four sporozoites, which are a form of the infectious parasite. The incubation period following exposure ranged from two to ten days, with an average of seven days. Following ingestion, the oocyst migrates to the small intestine, where it produces sporozoites. The sporozoites colonize the small intestine and multiply asexually in the extra cytoplasmic parasitophorous vacuoles (18).

Table 1

Bibliographical Annotation Analysis in Journals Identifying the Pathogens Widely

Title	Author(s)	Years	Groups of pathogens			
			Virus	Bacteria	Parasite	Fungi
Etiology of Diarrhea, Nutritional Outcomes, and Novel Intestinal Biomarkers in Tanzanian Infants	Gosselin, et al	2017	Rotavirus 8.9 % (11)	*E. coli* 5 % (5), *Shigella* 5.7 % (7), *Campylobacter* (1)	*Cryptosporidium* 7.3 % (9)	-
Detection of Acute Gastroenteritis Etiology in Hospitalized Young Children: Associated Factors and Outcomes	Jamie M, et al	2017	Rotavirus 33 % (70)	*C difficile* 9.8 % (10); *Shigella* (2); *Salmonella* (9); *Campylobacter* (2)	-	-
Etiology of Severe Acute Water Diarrhea in Children in the Global Rotavirus Surveillance Network Using Quantitative Polymerase Chain Reaction	Operario DJ, et al	2017	Rotavirus, Norovirus, Adenovirus, Astrovirus	*Shigella*. *Salmonella, Campylobacter*. *E. coli*	*Cryptosporidium*	-
Use of quantitative molecular diagnostic methods to assess the etiology, burden, and clinical characteristics of diarrhea in children in low-resource settings: a reanalysis of the MAL-ED cohort study	Platts-Mills, et al	2018	Adenovirus, Astrovirus, Norovirus, Rotavirus,	*Campylobacter, E. coli, Shigella,*	*Cryptosporidium*	-
Potential Diarrheal Pathogens Common Also in Healthy Children in Angola	Pelkonen T, et al	2018	Adenovirus 7 (4 %), Astrovirus 7 (4 %), Norovirus 43 (22 %), Rotavirus 40 (21 %), Sapovirus 22 (11 %)	*E. Coli* 100 (52 %), *Shigella* 29 (15 %), *Campylobacter* 29 (15 %), *Salmonella* 2 (1%)	*Giardia* 27 (14 %), *Cryptosporidium* 22 (11 %), *Entamoeba* 7 (4 %)	-
Bacterial and viral etiology of childhood diarrhea in Ouagadougou, Burkina Faso	Bonkoungou IJ, et al	2013	Rotavirus 85 (30 %), Adenovirus 14 (5 %),	*Shigella* 16 (6 %). *Salmonella* 24 (9 %), *Campylobacter* 5 (25). *E. coli* 67 (24 %)	-	-
Pathogen-specific burdens of community diarrhea in developing countries (MAL-ED): a multisite birth cohort study	Platts-Mills, et al	2015	Astrovirus, Norovirus, Rotavirus	*Campylobacter*, *E. coli*, *Shigella* -	*Giardia, Cryptosporidium*	
Etiology and Epidemiology of Diarrhea in Hospitalized Children from Low Income Country: A Matched Case-Control Study in Central African Republic	Breurec S, et al	2016	Adenovirus 37 (11.1 %), Astrovirus 48 (14.4 %) Norovirus 46 (13.8 %), Rotavirus 145	*E. coli* 72 (21.6 %), *Shigella* 94 (28.2 %), C	*Cryptosporidium* 51 (15.3 %), *Entamoeba* 11 (3.3), *Giardia* 29 (8.7 %)	-
Etiology of diarrheal disease and evaluation of viral–bacterial coinfection in children under 5 years old in China: a matched case–control study	Li L, et al	2016	Rotavirus 40.6 %, Norovirus 24.7 %, Adenovirus 10.9 %,	*Shigella* (18.6 %), *Salmonella, Campylobacter*	-	-
Real-time PCR identification of agents causing diarrhea in Rwandan children less than 5 years of age	Kabayiza JC, et al	2014	Rotavirus (42 %), adenovirus (39 %),	*E. coli* (21 %), *shigella* (13 %), *campylobacter* (14 %)	-	-
Real-Time PCR Threshold Cycle Cutoffs Help To Identify Agents Causing Acute Childhood Diarrhea in Zanzibar	Elfving K, et al	2014	Norovirus (19 %), rotavirus (9.1 %)	*Shigella* (20 %), *E. coli* (16 %)	*Cryptosporidium* (25 %),	-
Detection of 23 Gastrointestinal Pathogens among children who present with diarrhea	Stockmann C, et al	2017	Adenovirus (7 %), sapovirus (6 %), rotavirus (4 %), astrovirus (2 %)	*Clostridium difficile* (16 %), *E. Coli* (15), *Salmonella* (2 %), *Campylobacter* (1 %).	*Giardia* (4 %)	-

PCR: Polymerase Chain Reaction

Table 2

Diarrhea Pathogens Group

Virus	Bacteria	Parasite
-Rotavirus	-*Shigella spp*	-*Giardia lambia*
-Norovirus	-*Salmonella spp*	-*Cryptosporidium spp*
-Adenovirus	-*Campylobacter spp*	-*Entamoeba histolytica*
-Sapovirus	-*Escherichia coli*	
-Astrovirus	-*Clostridium difficile*	

Each cell multiplies rapidly, forming thick-walled oocysts capable of being excreted in the stool and surviving in the environment. Additionally, they create thin-walled oocysts that can automatically infect the patient. Three suggested mechanisms account for the symptoms: inflammatory cell invasion of the lamina propria: increased epithelial permeability, villous atrophy, and cell death, and malabsorption due to bowel architecture failure. Cryptosporidium can alter the host immune response to prevent infected cells from undergoing apoptosis, thus allowing the infection to continue (18).

The fungal pathogen group was not found in these 12 pieces of literature, but another study states that the cause of diarrhea in the fungal group is *Candida albicans*. *C. albicans* is rarely found because it causes canker sores more often than gastrointestinal infections. *C. albicans* are more easily infected when normal immunity is compromised (5).

The dominant study samples were less than five years old. Many cases of diarrhea are found at this age because the immune system in infants and toddlers (under five years old) is still learning to recognize and protect the body from incoming pathogens so that they are more susceptible to infection with the disease. Whereas in adolescents and adults, the immune system has recognized the type of pathogen and immediately responds when the pathogen will infect the body. Therefore, parenting, food hygiene, and children's nutrition play an essential role in preventing diarrhea (19,20).

To prove the etiology of the pathogen causing diarrhea requires accurate examination. In 12 research journals, only three laboratory tests were found, namely, PCR, culture, and serological tests. This microscopic examination is not used because microscopic examination can only see the presence of parasites and ova (eggs, cysts) in the feces. This makes fecal microscopic examination of high subjectivity, namely only in the parasite pathogen group, so it is rarely used to look for pathogens that cause diarrhea (21).

The PCR examination method is most widely used to determine the etiology of diarrhea in the research literature. PCR is a laboratory technique used to amplify specific DNA segments for a variety of laboratory and/or clinical applications. The main components of PCR are templates, primers, free nucleotide bases, and the DNA polymerase enzyme. PCR uses complementary base pairs, double-stranded properties, and the melting temperature of the DNA molecule. This process involves cycles through 3 sequential loops of temperature-dependent reactions: DNA fusion (denaturation), annealing, and enzyme-driven DNA replication (elongation) (22).

The authors expect that further research can be grouped by region, economy, geography, or risk factors so that they can draw more complete conclusions. The authors also hope that this literature review can be used as a contribution to medical science in the future.

CONCLUSION

In this study, it was found that the most common type of virus was Rotavirus. In the bacterial group, *Escherichia coli* is the bacterial pathogen that causes the most diarrhea. At the

same time, the most type of parasite found was *Cryptosporidium sp*. The age range of children who were more frequently sampled was 0-5 years. Of the 12 research articles identified, Polymerase Chain Reaction was used.

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A descriptive analysis of the spatiotemporal distribution of hepatitis A virus outbreak in Pacitan, East Java, Indonesia

Un análisis descriptivo de la distribución espacio-temporal del brote del virus de la hepatitis A en Pacitan, Java Oriental, Indonesia

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SUMMARY

Background: *Hepatitis A virus (HAV) is one of the most serious notifiable viral hepatitis and causing public health problems in Indonesia. The outbreaks of HAV in Indonesia have been reported in several sites from 1998-2018, however systematic epidemiological data regarding Spatio-temporal distribution of HAV outbreak are lacking. Aims: To explore, visualize, and report systematically the recent HAV outbreak and identify the socioeconomic determinants associated with the risk of HAV outbreak.*

Methods: *The study design was a retrospective cross-sectional study. Data on the incidence and distribution of HAV outbreak 2019 were collected from the database of CDC District Level Health Office of Pacitan. Maps were constructed using qGIS software to visualize the Spatio-temporal distribution of HAV outbreaks.*

Results: *Out of a total of 1 326 case records, 399 (30.1 %) were classified as probable cases of HAV, and 125 (9.4 %) as confirmed cases based on positive IgM Anti-HAV. Majorly the diagnosis was based on symptoms and exposures only, a limited number of tests was performed because testing capacity is insufficient. Majorly the cases occurred in sub-district that are*

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passed with the same river as source water in the community. The pattern of outbreak transmission is a common source. Linear regression analysis showed that proportion of low-level education (r= 1.34; p-value= 0.012), number of household (r= -1.08; p-value= 0.003), and population density (r= 1.87; p-value= 0.005) for each sub-district were significantly correlated with number of cases.

Keywords: *Geographic information system, hepatitis, epidemiological mapping.*

RESUMEN

Antecedentes: *El virus de la hepatitis A (VHA) es una de las hepatitis virales de declaración obligatoria más graves y causa problemas de salud pública en Indonesia. Se han notificado brotes de VHA en Indonesia en varios sitios entre 1998 y 2018; sin embargo, faltan datos epidemiológicos sistemáticos sobre la distribución espaciotemporal del brote de VHA.*

Objetivos: *Explorar, visualizar y notificar sistemáticamente el reciente brote de VHA e identificar los determinantes socioeconómicos asociados con el riesgo de brote de VHA.*

Métodos: *El diseño del estudio fue un estudio transversal retrospectivo. Los datos sobre la incidencia y distribución del brote de VHA 2019 se recopilaron de la base de datos de la Oficina de Salud de Pacitan a nivel de distrito de los CDC. Los mapas se construyeron utilizando el software qGIS para visualizar la distribución espaciotemporal de los brotes de VHA.*

Resultados: *De un total de 1326 expedientes de casos, 399 (30,1 %) se clasificaron como casos probables de VHA y 125 (9,4 %) como casos confirmados con base en IgM anti-VHA positivo. En su mayoría, el diagnóstico se basó únicamente en síntomas y exposiciones, se realizó un número limitado de pruebas porque la capacidad de prueba es insuficiente. La mayoría de los casos ocurrieron en sub-distritos que son atravesados por el mismo río como fuente de agua en la comunidad. El patrón de transmisión de los brotes es una fuente común. El análisis de regresión lineal mostró que la proporción de educación de bajo nivel (r= 1,34; valor de p= 0,012), el número de hogares (r= -1,08; valor de p= 0,003) y la densidad de población (r= 1,87; valor de p= 0,005) para cada subdistrito se correlacionaron significativamente con el número de casos.*

Palabras clave*: Sistema de información geográfica, hepatitis, mapeo epidemiológico.*

INTRODUCTION

Hepatitis A virus (HAV) is the most common widespread viral hepatitis and growing worldwide public health problems (1). WHO has reported nearly 1.4 million cases of hepatitis A worldwide every year, with approximately half of the cases occurring in the Asian region and endemic throughout most of South-East Asia. The viral hepatitis challenge is monumental and ironic, as the seventh leading cause of death (5.416 per year) in the world although HAV is completely preventable (2). HAV is a major public health issue globally that has not been prioritized until now (2,3). It was controlled by improvements in water, sanitation, and hygiene. However, multiple outbreaks of such preventable diseases are often reported throughout the region. The lack of consistent and credible data on the incidence of hepatitis and spread of HAV across subpopulations in South-East Asia hinders the development and monitoring of effective national policies to fight viral hepatitis (2).

The rate of infection is closely related to access to unsafe food or drinking water, inadequate sanitation, poor personal hygiene, and socio-economic factors such as population density, economic variables, and educational background (3,4). It has been shown that improvement of socio-economic status reduces the incidence of all types of viral hepatitis (3). In Indonesia, as a middle-income country, hepatitis A endemicity remains moderate-to-high and is connected to socio-economic disparities that contribute to different hygiene and sanitation standards being found in close proximity (Table 1) (5).

In 2010 there were 6 outbreaks with 279 cases, while in 2011 there were 9 outbreaks with 550 cases. In June 2012, there were 4 outbreaks with 204 cases. In 2018 there were 88 cases in Lamongan and Bangkalan, it has been assumed that poor hygiene and sanitation in canteens (no washbasins accessible) and the proximity of septic tanks to wells may have lead to the spread of HAV (4,6,8). Ministry of Health reported there were outbreaks in Pacitan (1 326 cases), and Depok (306 cases, 87 % is students) caused by contaminated food in the school canteen in 2019. The outbreak of HAV in Pacitan, East

Table 1

Outbreak hepatitis A virus in Indonesia

No.	Province	Districts	Total Case	Year	Ref (s)
1	West Java	Bogor	74	1998	(6)
2	East Java	Bondowoso	47	2004	(6)
3	East Java	Bondowoso	65	2006	(6)
4	Banten	Tangerang	17	2007	(6)
5	DI Yogyakarta	Yogyakarta	1 160	2008	(6)
6	East Java	Ngawi	146	2009	(6)
7	Riau	Bintan	87	2013	(7)
8	Lampung	Lampung Timur	11	2013	(7)
9	West Sumatera	Padang	15	2013	(7)
		Darmasraya	43	2013	(7)
10	Jambi	Jambi	26	2013	(7)
11	Central Java	Sukoharjo	26	2013	(7)
12	East Java	Pasuruan	110	2013	(7)
		Ponorogo	25	2013	(7)
		Lamongan	72	2013	(7)
		Jombang	14	2013	(7)
		Pacitan	66	2013	(7)
13	Bengkulu	Bengkulu	19	2014	(7)
14	West Sumatera	Sijunjung	159	2014	(7)
15	East Kalimantan	Paser	282	2014	(7)

Java Province (2019) which the highest number of HAV cases (1 326 cases) during the 1998-2019 period. The prevalence of hepatitis in East Java increased to 1 percent in 2013. Data from the Ministry of Health's Pusdatin recorded that there were 287 cases of HAV in East Java. Meanwhile, in 2013 there were 66 incidents in the Ngadirojo sub-district of Pacitan district mostly students were infected (7). The prevalence in the population in Pacitan as small towns (1 342.42 Km^2) is much higher than in the big cities (6). In low-income areas, the prevalence of infection is generally high, but the burden of disease is low, and HAV is not perceived to be a major public health issue (8). Pacitan had experienced an HAV outbreak in 2013, it is certainly a problem and challenge for the government. The transmission is direct contact with an infected person, thus, the population density in the region needs to be studied through mapping to prevent repeated outbreaks in the future.

Even though several incidences of HAV outbreaks in Indonesia had been reported in the last decade, according to our knowledge there are no available maps of HAV outbreak mapping to show their spatial distribution and attack rate/incidence proportion. Mapping the epidemiological distribution and incidence of HAV outbreaks will help to identify vulnerable communities and socioeconomic determinants where outbreaks pose significant threats and allocate the resources for their disease control and prevention. Since Pacitan had experienced an HAV outbreak twice in 2013 and 2019, it is important to analyze and explore the

variation of outbreak geographical locations and socioeconomic determinants. Moreover, this study is vital to provide an informed decision-making process for the local government leading to better control and prevention of HAV outbreaks in the study area.

Maps are valuable instruments for epidemiological research analysis and are especially effective in transmitting important public health messages to a wide range of audiences (8). The importance of creating an epidemic distribution map is to study the variables that have an impact on the agent, host, environment, and geography that are very helpful in trying to execute the strategy accordingly (4). A geographic information system (GIS) was used to analyzing and studying the epidemiological spread of a number of infectious diseases or outbreaks. GIS also has been used to assess the spatial and temporal patterns of outbreaks and to classify risk areas or areas of concern for the outbreak in a specific area (4). The present study aimed to report the recent HAV outbreak in the study area (Pacitan, East Java Province) and identify the socioeconomic factors associated with the risk of HAV infection in the study area using GIS-based approach analysis.

MATERIALS AND METHODS

Study population / Sample

This study was a retrospective cross-sectional observational study during hepatitis A outbreak in Pacitan, East Java, Indonesia occurred between May and October 2019. HAV outbreak data were collected from the database of CDC District Level Health Office of Pacitan. The outbreak investigation was conducted one day after the outbreak by the District Level Health Office (Dinas Kesehatan) of Pacitan. A clinically suspected case was defined as any individuals with acute symptoms including those with clinical manifestation of hepatitis were recruited and recorded. An acute clinical manifestation was defined by the onset of acute illness with a minimum of two of the following clinical symptoms: fever, malaise, flatulence, anorexia, nausea, vomiting, dark or tea-colored urine, and jaundice between May and October 2019.

A probable case was defined in the presence of jaundice/or elevated serum alanine aminotransferase (ALT/AST) more than twice the upper limit of normal or 80 IU/L in a suspected case. A confirmed case was defined as a suspected or probable case that was shown a positive result for anti-HAV IgM. The human population of the study districts, population density, household units, education categories, toilet ownership, and disparity economy value was collected from the District Central Bureau of Statistics in 2016 based on the census conducted in 2015.

Data Collection

The trained public health officers from the hospital and PHCs dedicated to the outbreak data collection and compilation input the data to the electronic case report form. The baseline characteristics of patients were collected comprising demographic, clinical, and laboratory data. Demographic data including gender, age, and address were collected. Clinical data including the status of admission (outpatient or inpatient) and clinical symptoms were recorded. Laboratory data were also compiled.

The Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya had approved the research protocol. Patient consent was not required to review their medical records because the research has no more than minimal risk to the subjects. Research and data access protocol was also approved by the Center for Disease Control and Prevention (CDC) – District Level Health Office (Pengendalian dan Pemberantasan Penyakit / P2 Dinas Kesehatan) of Pacitan.

Statistical analysis and geographical mapping

We performed the descriptive analysis of the data. The comparison between two groups was conducted using the Student T-test or Mann Whitney for continuous data, and Chi-square or Fisher Exact test for categorical data. The demographic and socioeconomic data for each sub-district was collected from the Central Bureau of Statistics in 2019. Statistical analysis was conducted using SPSS v.19 (IBM Corp., NY, USA) and statistical analysis was significant if p-value < 0.05.

To demonstrate geographical variability and hepatitis A incidence, we also mapped sub-district-specific incidence using QGIS 2.18.10 (GNU General Public License, OSGeo Foundation).

Risk factor analysis

HAV outbreak is a multi-factorial viral infectious disease that is strongly associated with socioeconomic determinants. HAV cases have been reported in several varieties of settings from urban to remote rural areas with low socioeconomic status. HAV outbreaks are also considered a disease of poverty in middle and low-income areas with several determinants including high population density, lack of flushed toilets, low education level, high regional disparity index, and a number of household units in a certain area (9-11). The probability of HAV occurrence can be calculated from 5 socioeconomic variables using the Pearson correlation coefficients and their associations obtained in SPSS version 19.0 (IBM Corp, NY, US).

RESULTS

Epidemiologic Characteristics of the HAV Outbreak

In this study, we collected surveillance data of HAV infections in Pacitan, East Java Province during the outbreak from May to October 2019, and collected a number of socioeconomic variables to determine the geographic distribution of HAV outbreaks.

Among a total of 1 326 case records (Table 2), 399 (30.1 %) were classified as probable cases of HAV, and 125 (9.4 %) as confirmed cases

Table 2

Key findings from CDC – District Level Health Office of Pacitan, East Java, Indonesia

No.	Parameters (n= 1 326)	Total (%)	Percentage
1.	Age [mean±SD (years)]	34.5 ± 15.2	
	Age group, y.o [n(%)]		
	0 - 5	6	0.5
	6 - 18	232	18.8
	19 - 60	936	75.7
	> 60	62	5.0
2.	Gender [n (%)]		
	Male	716	54.0
	Female	610	46.0
3.	Symptoms [n (%)]		
	Fever	1236	93.2
	Nausea	1261	95.1
	Tea-colored urine	1257	94.8
	Jaundice	1170	88.2
4.	Laboratory parameters [median± IQR (U/L)]		
	AST	402 ± 515	-
	ALT	488 ± 343	-
5.	Status of cases [n (%)]		
	Clinically-suspected	927	69.9
	Probable	274	20.7
	Confirmed	125	9.4
6.	Patient Outcomes [n (%)]		
	Inpatient	514	38.8
	Outpatient	810	61.1

based on positive IgM Anti-HAV. Majorly the diagnosis is based on symptoms and exposures only, a limited number of the test was performed because testing capacity is insufficient to meet current needs.

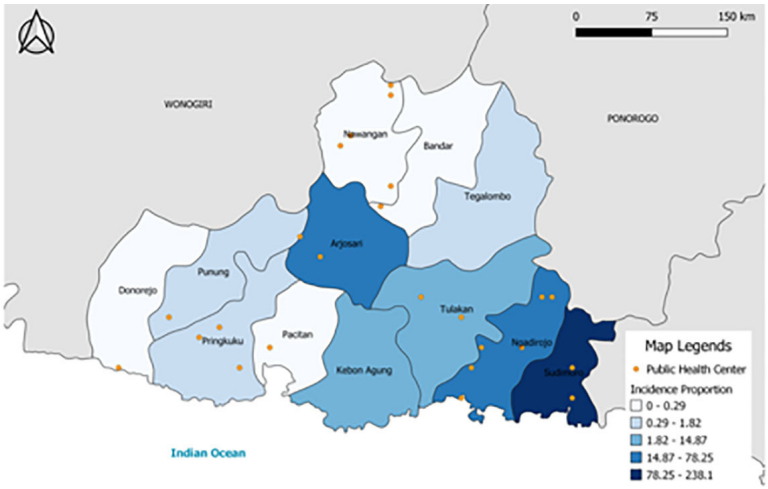

Figure 1. Clinically-reported HAV outbreak cases in Pacitan, East Java, Indonesia 2019.

The majority of cases were male, which accounted for 54.0 % of all clinically suspected cases. Most case-patients were 19 to 59 years of age (75.7 %), 0.5 % were aged 5 years or younger, 18.8 % were aged 6 to 18 years, and 5 % were aged 60 years or older. Most of the cases were managed in an outpatient setting (61.1 %). The laboratory results from the probable cases showed median serum AST level 402 U/L and ALT level 483 U/L. Almost 90 % of cases, reported classical symptoms of HAV infection.

Table 3

Clinically-suspected HAV cases based on reported sub-district in Pacitan, East Java, Indonesia

No.	Sub-districts	Total [n (%)]	Hospitalizations [n (%)]	Attack rate (%)
1.	Sudimoro	734 (55.3)	149 (20.2)	2.381
2.	Ngadirojo	362 (27.3)	269 (74.3)	0.782
3.	Tulakan	116 (8.7)	33 (28.4)	0.148
4.	Arjosari	86 (6.5)	34 (39.5)	0.218
5.	Kebonagung	13 (1.0)	4 (30.7)	0.030
6.	Tegalombo	9 (0.7)	7 (77.7)	0.018
7.	Punung	2 (0.2)	2 (100)	0.005
8.	Pacitan	2 (0.2)	1 (50)	0.001
9.	Donorojo	1 (0.1)	1 (100)	0.003
10.	Pringkuku	1 (0.1)	0	0.006
	Total	1 326 (100)	500 (37.7)	0.240

According to sub-districts that reported the HAV outbreak (Figure 1, Table 3), majorly the cases were reported in Sudimoro sub-districts, followed by Ngadirojo, and Sukorejo. However, hospitalized cases were reported mostly by Ngadirojo sub-districts. Based on the interview, Sudimoro has poor hygiene and a healthy lifestyle compared to other sub-districts. There have been 171 ODF villages in Pacitan, the most recent being the Sudimoro sub-districts.

Temporal distribution of HAV outbreak

We found a person-to-person spread as the main apparent transmission route of the HAV infection. HAV outbreak in Pacitan rapidly spread from a single sub-district to others in just 60 days. Based on the interview, the first case with clinically fever, icteric, and abdominal pain occurred in the Sudimoro sub-district on May 8th, 2019. The surveillance team found 60 cases with the same sign and symptom in other sub-district (Ngadirojo, Sukorejo, Tulakan). Geographically, the Kaligoro river in Sukorejo as source water in the community passes through the HAV outbreak area. Based on water sample inspection this river was containing an increase of E. coli that contaminated household waste. In the dry season, the area had difficulty accessing clean water.

Based on the epidemiological curve (Figure 2), the pattern of outbreak transmission is a "common source" that occurs in the Ramadhan period (May 2019), people usually buy food or water for iftar that may be contaminated. The sudden increase in the number of cases is reported after the Islamic Id Al-Fitr holiday (June 2019). In the Arjosari public health center, 71 cases (82 %) occurred in Pondok Pesantren Tremas that infected children aged 11-19 years. Arjosari has the longest duration of incidence it is around 4 months. The incidence of the outbreak was decreasing in the rainy season in November 2019.

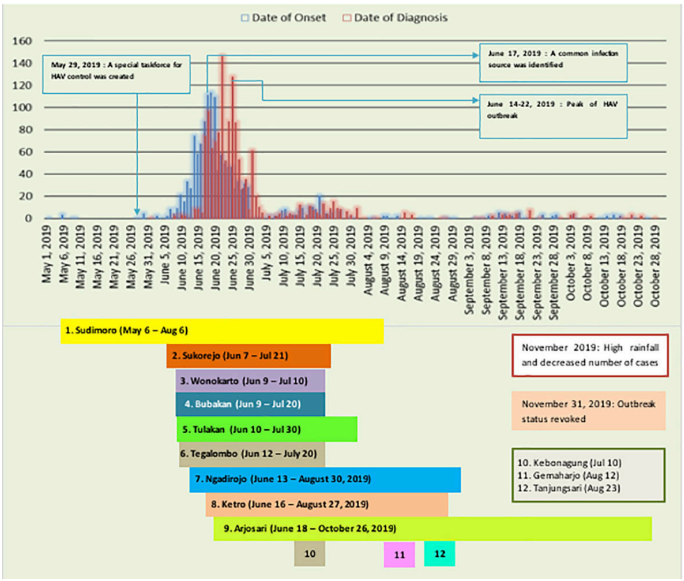

Figure 2. Outbreak curve of HAV cases in Pacitan, East Java, Indonesia

Pearson correlation matrix of socioeconomic determinants and modeling approach in HAV outbreak

The final set of socioeconomic determinants are the number of households, the proportion of household toilet ownership, the proportion of low-level education, regional disparity index, population density. We conducted Pearson correlation matrix analysis for all variables. The highest correlation coefficient is between numbers of households and regional disparity

index (0.958) followed by proportion of low-level education and population density (-0.874). However, we found significant multicollinearity among variables.

Linear regression analysis is often used to determine the probability and significance of a dependent variable based on one or several independent variables. The dependent variable represents the attack rate of HAV outbreak in a sub-district. The independent variables are a set of socioeconomic factors thought to associate with the distribution of HAV cases. Our results showed that proportion of low level education (r= 1.34; p-value= 0.012), number of household (r= -1.08; p-value: 0.003), and high population density (r= 1.87; p-value= 0.005) for each sub-district were significantly correlated with number of cases.

DISCUSSION

The incidence of HAV cases varies geographically within the study area (Pacitan District, East Java Province, Indonesia). The overall incidence of diagnosed HAV cases was 0.24 % and mainly occurred in the Sudimoro sub-district with an attack rate of 2.38 % (734 cases in 30 825 total populations) then followed by Ngadirojo with an attack rate of 0.78 %. It had already been recognized that hepatitis A is strongly related to the socio-economic and environmental factors of a country or region (12). In developing countries, such as Indonesia and several parts of Asia, hepatitis A is categorized as high endemicity (8). Several studies reported the relationship among socioeconomic variables with hepatitis A risk, including the education level, the gross domestic bruto, population density, toilet ownerships, and environmental hygiene (5,9,12,13).

Socio-economics determinants associated with HAV outbreak risk included in this study were a number of households, the proportion of household toilet ownership, the proportion of low-level education, regional disparity index, population density. The associations between these determinants and HAV risk showed significant results. The results of the analysis in this study show that the lower the educational level of the population and the higher the population density, the greater the attack rate of hepatitis A. The result means that the lower the socioeconomic level of a region, the more susceptible the adults will be infected by Hepatitis A. This finding is consistent with other studies (9,10,12,14). In Assis Brazil, for example, the poorer socioeconomic conditions (i.e. low education level) the higher the hepatitis A infection risk and this connection were statistically significant (9).

Based on surveillance data of the HAV outbreak in Pacitan, the majority of cases were male. It is a similarity to previous studies of Hepatitis A cases in Jember (2013) and Bondowoso (2016). Men have a lower awareness of their healthy lifestyle and more often consume food outside the home (4). Most cases in Pacitan were young adults, related with studies in Kerala, India at 2017 were 81 % in adults/young adults (15). In the Arjosari sub-district, most young adult cases occurred in boarding schools. Studies in Cirebon (2018), there were risk factors of hepatitis that occur in boarding school, such as the habit of washing cutlery without soap, using cutlery, and drinking together (16). From the cutlery used together were likely transmission of the disease occurs. The most dominant variables are eating together in one place and snack habits (17). Young adults have a high level of mobility and habit of snack outside the home, are lack in behaving in a clean and healthy life. They also in overseas areas where they live with their friends, and the level of interaction with each other is also high (18).

Majorly the cases were reported by the Sudimoro sub-district, this area was the eastern boundary of Pacitan, and far from urban development (19). The inaccessible health facilities and slow information in rural areas also tend to make people hard to come to health facilities, people are constrained by access, such as geographical access, length of travel, and transportation (20). From geological factors, it is considered much more difficult to get clean water sources (21). In Southern Sumatra (2000), there is a water-borne hepatitis A outbreak that infected individuals were more likely to have consumed water from a public well, and more likely to have used a dry pit outside their house for human waste disposal (5).

In a rural area like Pacitan, community outbreaks owing by poor hygiene and sanitary

practices (5). HAV virus spreads through food or water contaminated with the feces of infected people (4). Soil and water are places where the HAV virus can remain stable for a long time, especially during the rainy season, which probably helps the virus to percolate along with water to contaminate wells (15). Another case in Central Java shows a significant correlation between hepatitis A and water source because the transmission is through contaminated food or drink, that contain the virus from water with poor environmental conditions (14). Studies in an economically disadvantaged area in southern China, Yujia village reports in developing areas with poor living conditions such as an inadequate water supply, poor sewage facilities, and substandard sanitary conditions, the level of HAV transmission within the community is high (13).

Based on data, HAV outbreak Pacitan rapidly increase during Ramadhan (May 2019) and after Eid al-Fitr (June 2019) public holiday (Figure 2). The sudden increase in numbers of hepatitis A cases can be associated with socioeconomic status, sanitation, and lack of access to safe drinking water (22). Culturally, Ramadhan's largest and one of the most important holidays of the year, which usually followed with returning people to their family/hometown and cultural visitation to the neighborhoods for celebrating Id Al-Fitr by eating together. People tend to share the food without considering the hand and food hygiene, and also the source of food material that is used. The practice of poor hand washing is also a risk factor because it results in a risk of HAV entering the body when eating becomes large (4). Studies show that people who frequently purchased outside food have a higher risk (5).

The epidemiology of Hepatitis A outbreaks in Indonesia as developed countries remain moderate-to-high and is linked to socioeconomic differences (23) that lead to different standards of hygiene and sanitation is found (5). Based on East Java Regional Development and Planning Agency (BAPPEDA JATIM) data 2018. The number of people with poor economic levels in 2017 in Pacitan was recorded at 85 260 people (24). East Java was dominated by the elderly who had low education like primary school and under (25). The average education level of age 15 and over as much as 67.97 percent have graduated from primary or secondary school (24). People with a lower level of education have the possibility of morbidity caused by an unhealthy lifestyle and poor prevention action (25).

CONCLUSION

Based on our analysis of the HAV outbreak, we identified the distribution and incidence of HAV outbreak in the study area. The importance of socioeconomic determinants and values of Geographic Information System in the mapping the epidemiological distribution and incidence of HAV outbreak.

Conflict of Interest

The authors have no conflicts of interest in this study.

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Characteristics of patients with dengue hemorrhagic fever and its relationship with the prevalence of dengue shock syndrome in children

Características de los pacientes con fiebre hemorrágica por dengue y su relación con la prevalencia del síndrome de shock por dengue en niños

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SUMMARY

Introduction: *Many dengue hemorrhagic fever (DHF) cases tend to increase from year to year. This study aims to determine DHF patients' characteristics and determine their relationship with the prevalence of Dengue Shock Syndrome (DSS) throughout children.*
Methods: *This was a retrospective study using secondary data from medical records at Siti Khodijah Hospital, Indonesia, from 2012 to 2016.*
Results: *Among 963 patients, most patients were in the 5-13 years group (72.4 %), balanced male and female, at good nutritional status (71.8 %), the parental education 74.7 % of high school students. The history of dengue fever before was 2.5 %, and those with multiple infections were 17.8 %. The lowest platelet value of 41.4 % in the range $5x10^4$-1 $x10^5$, followed by a range of $2x10^4$-<$5x10^4$ of 30.8 %, the percentage increase in hematocrit (HCT) in the range 1-10 % (41.1 %), 11-<20 % (29.9 %) and ≥20 % by 27.3 %. The discharge status was 97.7 % cured, 1.5 % died, and 0.8 % referred. The diagnosis of non-shock DHF was 83.7 % and 16.2 % DHF with shock. There were significant correlation in children's characteristics with DHF with prevalence of DSS including nutritional status (p=0.001), parental education (p=0.036), history of dengue fever (p=0.001), platelet value (p=0.001), the percent increase in HCT (p=0.001), and discharge status (p=0.001).*
Conclusion: *Nutritional status, parental education, history of DHF, lowest platelet value, the percent*

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increase in hematocrit value, and the patient's discharge status were associated with the prevalence of DSS.

Keywords: *Hemorrhagic, dengue, shock, syndrome, children.*

RESUMEN

Introducción: *Muchos casos de dengue hemorrágico (DH) tienden a aumentar de año en año. Este estudio tiene como objetivo determinar las características de los pacientes con dengue hemorrágico y determinar su relación con la prevalencia del síndrome de choque por dengue (SDE) en los niños.*
Métodos: *Este fue un estudio retrospectivo que utilizó datos secundarios de registros médicos en el Hospital Siti Khodijah, Indonesia, de 2012 a 2016.*
Resultados: *Entre 963 pacientes, la mayoría de los pacientes se encontraban en el grupo de 5-13 años (72,4 %), hombres y mujeres equilibrados, en buen estado nutricional (71,8 %), la educación de los padres 74,7 % de los estudiantes de secundaria. El antecedente de dengue antes era del 2,5 % y los que tenían infecciones múltiples eran del 17,8 %. El valor de plaquetas más bajo de 41,4 % en el rango de $5x10^4$-1 $x10^5$, seguido de un rango de $2x10^4$- $<5x10^4$ de 30,8 %, el porcentaje de aumento en el hematocrito (HCT) en el rango de 1-10 % (41,1 %), 11- <20 % (29,9 %) y ≥20 % en 27,3 %. El estado de alta fue 97,7 % curado, 1,5 % fallecido y 0,8 % referido. El diagnóstico de dengue hemorrágico sin shock fue del 83,7 % y del 16,2 % de dengue hemorrágico con shock. Hubo una correlación significativa en las características de los niños con el dengue hemorrágico con la prevalencia de SSD, incluido el estado nutricional (p=0,001), la educación de los padres (p=0,036), los antecedentes de dengue (p=0,001), el valor de plaquetas (p=0,001), el porcentaje aumento de HCT (p=0,001) y estado de alta (p=0,001).*
Conclusión: *El estado nutricional, la educación de los padres, los antecedentes de dengue hemorrágico, el valor más bajo de plaquetas, el porcentaje de aumento en el valor del hematocrito y el estado de alta del paciente se asociaron con la prevalencia de DSS.*

Palabras clave: *Hemorrágico, dengue, shock, síndrome, niños.*

INTRODUCTION

The prevention of dengue infection in Indonesia has yielded satisfactory results through efforts to improve case management, vector control through mosquito breeding programs, and community mobilization to clean the environment (1). As similar to other infections such as *Helicobacter pylori*, the environment was an important factor in dengue infection (2). Since twenty years ago, the Ministry of Health of the Republic of Indonesia, assisted by professional organizations, has made guidelines for diagnosing and managing dengue infection so that the mortality rate of 46 % in 1968 could be reduced to <1 % in 2013. Also, by using integrated criteria of WHO 2009 and 1997, update management of Dengue Shock Syndrome in Pediatric cases can improve clinical management to reach the lower mortality until CFR <1 % (3,4). However, if we look at the disease's incidence, the number of dengue cases increases with increasing spread. This increase also occurs in other countries, especially tropical countries around the equator (5-7).

It is estimated that every year around 50 million people are infected with the dengue virus, of which 500 000 require hospitalization, and almost 90 % of inpatients are children. Southeast Asia, with a population of around 1.3 billion, is an endemic area (7). Indonesia, along with Bangladesh, India, Maldives, Myanmar, Sri Lanka, Thailand, and Timor Leste, falls into endemic A (high endemic). In that country, dengue is the main reason for hospitalization and one of the leading causes of death in children (5). Over six years, 13 940 patients were treated, consisting of 5 931 dengue fever (DF), 5 844 dengue hemorrhagic fever (DHF), and 2 165 dengue shock syndrome (DSS) patients (5). The highest age group is 5-14 years, namely 9 036 (64.8 %). The percentage of death cases of dengue infection is 0.08 % DF, 0.36 % DHF, and 7.81 % DSS (7).

The most common cause of death is in the DSS group. In addition to shock cases that cause death, it has also been reported in some cases of unusual clinical manifestations such as dengue encephalopathy, disseminated intravascular coagulation, and some cases accompanied by comorbidities such as Human Immunodeficiency Virus (HIV) infection and sepsis (8,9). Clinical manifestations of dengue virus infection are extensive can be asymptomatic/symptomatic, fever that is not typical/challenging to distinguish from other viral infections, DF, DHF, and expanded dengue syndrome/organopathy

(unusual clinical manifestations). DHF itself is distinguished from dengue fever by the presence of plasma leakage and categorized with non-shock DHF and DHF with shock (DSS) (9,10).

Siti Khodijah Hospital, Sepanjang, is a type B hospital located in Sidoarjo, Indonesia. Like most hospitals in East Java, Siti Khodijah Hospital, Sepanjang, in Indonesia also treated dengue cases in the top 10 most diseases, especially in children. Data from the Siti Khodijah Hospital Medical Record recorded with dengue and dengue fever diagnosis in patients with children for five years from 2012 to 2016 tend to increase (data not shown). Seeing the number of dengue cases and the tendency to increase, this study aims to conduct initial research on DHF patients' characteristics and their relationship to the prevalence of shock in children.

METHODS

This study is retrospective, using secondary data from medical records at Siti Khodijah Hospital, Indonesia, from 2012 to 2016. The data were collected for six months from July to December 2018. Diagnosis of DHF with or without shock was taken from the medical record when the patient returns from the hospital, and this is done by the physicians who are treating the patients. Descriptive analysis was used to determine the characteristics and distribution of samples, namely percent increase in hematocrit, lowest platelet value, age, sex, nutritional status, parental education, previous history of dengue pain, multiple infections, and patient status out of the hospital. A statistical test to assess the relationship between the patient characteristics and DSS events' prevalence was carried out using the Spearman correlation test.

RESULTS

Within five years, a total sample of pediatric patients diagnosed with DHF in the medical record of 1 015 sufferers was obtained. After the recapitulation, 52 medical records were obtained, with laboratory data not attached, so they were excluded from the study sample. So that the number of samples studied is 963. Characteristics of children with DHF are shown in Table 1. The characteristics were age, sex, nutritional status, parental education, previous history of dengue fever, multiple infections, lowest platelet value, the percent increase in hematocrit, discharge status, and patient diagnosis.

Table 1

Characteristics of children with DHF

Patient characteristics	Category	Frequency	Percentage
Age	1 month - <1 year	59	6.1
	1 year - <5 year	207	21.5
	5 year - 13 year	697	72.4
Sex	Male	499	51.8
	Female	464	48.2
Nutritional status	Good	691	71.8
	Deficient	124	12.9
	Poor	23	2.4
	Excess	125	12.9
Parental education	Elementary school	36	3.7
	Junior high school	80	8.3
	Senior high school	719	74.7
	University	128	13.3

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…continuation of Table 1.

Patient characteristics	Category	Frequency	Percentage
Previous history of dengue fever	Yes	24	2.5
	No	939	97.5
Multiple infections	Yes	24	2.5
	No	939	97.5
Lowest platelet value	$<2x10^4$	95	9.9
	$2x10^4$-$<5x10^4$	297	30.8
	$5x10^4$-$1x10^5$	399	41.4
	$>1x10^5$	172	17.9
Percent increase in hematocrit	1-10 %	396	41.1
	11-< 20 %	288	29.9
	≥20 %	263	27.3
Discharge status	Lab Exam 1x	16	1.7
	Heal	941	97.7
	Died	14	1.5
	Referred	8	0.8
Patient diagnosis	DHF without shock	806	83.7
	DSS	157	16.3

DHF: Dengue Hemorrhagic Fever

The statistical analysis of characteristics of patient's correlation with DSS genesis prevalence is shown in Table 2. Patients' characteristics with significant results were age, nutritional status, parent education, history of dengue pain, low platelet values, percentage of hemoconcentration, and patients' discharge status.

Table 2

Characteristics of patients correlation with DSS genesis prevalence

Characteristics	Correlation coefficient Spearman's rho	Sig. (2-tailed)
Age	.052	.109
Sex	-.032	.325
Nutritional status	.120**	.000
Parental education	-.068*	.036
Previous history of dengue fever	.110**	.001
Multiple infections	.043	.180
Lowest platelet value	-.202**	.000
Percent increase in hematocrit	.295**	.000
Discharge status	.290**	.000

**Correlation is significant the 0.01 level (2-tailed)
*Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

This study revealed that nutritional status, parental education, history of DHF, lowest platelet value, and the percent increase in the patient's hematocrit value and discharge status were associated with the prevalence of DSS events. The number of malnutrition found was only 22 cases (<0.01 %) of the total population in 2014 of 2 104 912 people in Sidoarjo, Indonesia (11). A 2013 meta-analysis with nine studies examined found an association between malnutrition and DSS events (OR: 1.19, 95 % CI: 1.00-1.41). This meta-analysis also conducted an analysis looking for a normal nutritional relationship with DSS, where the results obtained are the opposite relationship between normal nutritional status with DSS events (OR: 0.87, 95 % CI: 0.77-0.99) (12). Based on the same meta-analysis, eight existing studies concluded that obesity/overweight is not related to DSS incidence (OR: 1.31, 95 % CI: 0.91-1.88) (12). However, a report concluded that overweight/obesity was one of the prognostic factors in severe dengue infection in children (13). DSS is more common in immunocompetent children and good nutritional status than in immunocompromised children. Whereas in malnutrition, DSS is very rare (14). Good nutritional status is associated with a good immune response which can cause severe DHF (15). Another researcher also has the same opinion that there is no significant difference between good nutritional status and malnutrition on DSS events in children (16-18).

Moreover, it can also explain that most parents' education level was 74.7 % of senior secondary, followed by tertiary education 13.3 %, junior high school, 8.3 %, and elementary school, 3.7 %. This shows knowledge level of most parents of DHF patients was quite good. A report also stated that parents' level of knowledge plays an essential role in the behavior of prevention of DHF (19). For data on education distribution according to Regional Government Administration Report of Sidoarjo Regency, Indonesia. In 2014, even most of the tertiary education level population was 54.9 %, followed by senior high school at 20.3 %, junior high school at 11.4 %, and elementary/equivalent 13.3 % (11). A study concluded that prevention of DHF shock might be achieved through health education interventions in the form of counseling. It might improve parents' cognition and affection aspects (knowledge and attitude) of dengue fever in doing self-care and prevention (20).

Secondary data about the history of ever having dengue fever was found to be very small. It is said that the first infection (primary) causes lifelong immunity to the cause serotype, for secondary infections with different viral serotypes (secondary heterologous infection) generally provide more severe clinical manifestations than primary infection (5).

DSS often occurs when the platelet count $<5x10^4/mm^3$ (16,21,22). The previous study stated that a negative relationship was found in platelet counts conducted by 37 studies (12). So the lower the platelet count and the higher the hemoconcentration, especially ≥20 %, contribute significantly to DSS occurrence (10). This is the basis of the diagnostic criteria for DHF diagnosis by WHO.

Hemoconcentration is defined by an increase in hematocrit >20 % of the standard value based on age. Patients with hematocrit levels at admission >42 % are twice as likely to experience shock than <42 % (22,23). In this study, the essential diagnosis used was the diagnosis of dengue patients recorded in medical records. Thus, the stated diagnosis of the patient is the treating physician. If the diagnosis of DHF is recapitulated, but it is not supported by platelet reduction data $<1x10^5$ or hemoconcentration incidence ≥20 %, then the assumption that doctors diagnose the clinical criteria for dengue fever is very likely to be biased with the diagnosis of DF (22). This is one of the weaknesses of this study, where the diagnosis was determined based on the Medical Record records that the doctor made.

Of the 14 DHF cases that died, 13 cases were diagnosed with dengue with shock, and from 8 complex cases of DHF referred to, six were diagnosed with dengue with shock. If shock occurs, the body first compensates (compensated shock). Severe bleeding that occurs causes a decrease in hematocrit, and the number of leukocytes that originally leukopenia can increase as a stress response in patients with severe bleeding. Some patients enter the critical

phase of plasma permeation and then experience shock before the fever falls, in which the increase in hematocrit and thrombocytopenia occur very quickly. Besides, in DHF patients accompanied by shock or organ involvement cannot occur, such as severe hepatitis, encephalitis, myocarditis, and/or severe bleeding. This is known as expanded dengue syndrome (5,14).

The age range in this study is between 5 years to 13 years. The previous research stated that the age factor influences dengue infection patients to experience DSS, and it explained 17 % of DHF patients experienced DSS, and the proportion of the most significant incidence was experienced by the age group of fewer than five years (58.8 %) (24). Babies aged 6-12 months have a more severe risk, even in primary infections (5,25). A study meta-analysis concluded that the pooling of odds ratios from several studies showed a negative relationship between age and DSS events (OR: 0.50, 95 % CI: 0.36-0.70) (12,24,26).

Sex characteristics in the sample distribution were almost the same at 51.8 % and 48.2 % female. It can be assumed that the number of males and females and the level of activities inside and outside the home were not much different. According to a previous study with multiple samples, it was concluded that the prevalence by sex did not reveal any significant differences between women and men (15,22,27). Therefore, a study meta-analysis showed that there was a significant relationship between female sex and DSS (12).

CONCLUSION

Nutritional status, parental education, history of DHF, lowest platelet value, the percent increase in hematocrit value, and the patients' discharge status were associated with the prevalence of DSS events.

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Conflicts of Interest

The authors declare no conflict of interest.

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ARTÍCULO ORIGINAL

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Effects of treadmill exercises on pancreatic β cell function through the role of vitamin D in patients with type 2 diabetes mellitus

Efectos de los ejercicios de la cinta de correr sobre la función de las células β pancreáticas a través del papel de la vitamina D en pacientes con diabetes mellitus tipo 2

Anugrahini Irawati [1*], Sony Wibisono Mudjanarko[2*,**•], Damayanti Tinduh[3***]

SUMMARY

Background: *Vitamin D is a lipophilic compound that can be trapped in adipose tissue that is often obtained in metabolic syndrome. This study aims to compare 25(OH)D levels and pancreatic β cell function before and after moderate-intensity treadmill with increased speed and gradual inclination in type 2 diabetic patients.*
Method: *In this quasi-experimental trial with a pretest-posttest design, 22 patients with T2DM were divided into 2 groups: the exercise group and the control group. Participants were assessed for clinical and biochemistry. Serum insulin, fasting blood glucose, 25(OH)D, and HOMA B were calculated. All measurements were performed at the beginning and after 4 weeks of training.*
Results: *Vitamin D levels before and after the treadmill in the exercise group were 19.22 ± 4.06 ng/mL and 21.74 ± 4.53 ng/mL, respectively. While vitamin D levels before and after the treadmill in the control group were 21.71 ± 4.22 ng/mL and 23.25 ± 5.46 ng/mL, respectively. Vitamin D levels before and after the treadmill in the exercise group were significantly increased (p= 0.041) but not in the control group (p= 0.355). A significant improvement that was observed in the homeostatic model assessment of β cell function (HOMA B) was both significantly ameliorated (p= 0.013 and p= 0.032, respectively).*

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Conclusion: *Moderate intensity treadmill exercises with increased speed and gradual inclination can increase vitamin D levels and pancreatic β cell function.*

Keywords: *HOMA B, treadmill, type 2 diabetes mellitus, 25(OH)D*

RESUMEN

Antecedentes: *La vitamina D es un compuesto lipofílico que puede quedar atrapado en el tejido adiposo que se obtiene a menudo en el síndrome metabólico. Este estudio tiene como objetivo comparar los niveles de 25 (OH) D y la función de las células β pancreáticas antes y después de la cinta de correr de intensidad moderada con mayor velocidad e inclinación gradual, en pacientes diabéticos Tipo 2.*
Método: *En este ensayo cuasiexperimental con un diseño pretest-postest, 22 pacientes con DM2 se dividieron en 2 grupos: el grupo de ejercicio y el grupo de control. Los participantes fueron evaluados en términos clínicos y bioquímicos. Se calculó la insulina sérica, la glucemia en ayunas, la 25 (OH) D y el HOMA B. Todas las mediciones se realizaron al inicio y después de 4 semanas de entrenamiento.*
Resultados: *Los niveles de vitamina D antes y después de la cinta de correr en el grupo de ejercicio fueron 19,22 ± 4,06 ng/mL y 21,74 ± 4,53 ng/mL, respectivamente. Mientras que los niveles de vitamina D antes y después de la cinta en el grupo de control fueron 21,71 ± 4,22 ng /mL y 23,25 ± 5,46 ng/mL, respectivamente. Los niveles de vitamina D antes y después de la cinta de correr en el grupo de ejercicio aumentaron significativamente (p = 0,041) pero no en el grupo de control (p= 0,355). Una mejora significativa que se observó en la evaluación del modelo homeostático de la función de las células β (HOMA B) mejoró significativamente (p= 0,013 y p= 0,032, respectivamente).*
Conclusión: *Los ejercicios en cinta de correr de intensidad moderada con mayor velocidad e inclinación gradual pueden aumentar los niveles de vitamina D y la función de las células β pancreáticas.*

Palabras clave: *HOMA B, cinta rodante, diabetes mellitus tipo 2, 25 (OH) D*

INTRODUCTION

Diabetes mellitus (DM) is a global health burden affecting 285 million (6.4 %) people over the world, costing $367 billion annually. Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality in 90 % to 95 % of all diabetic cases. The number of T2DM patients is expected to rise to 300 million by 2025 (1). Vitamin D seems to act to maintain many of the sequential events that enable the β-cells located in the pancreatic islets of Langerhans to release the insulin necessary to control blood levels of glucose (2). Vitamin D has both direct and indirect effects, the latter via regulation of calcium effects on various mechanisms related to the pathophysiology of type 2 diabetes, including pancreatic beta-cell dysfunction, impaired insulin action, and systemic inflammation. Recently, vitamin D receptor (VDR) and vitamin D-metabolizing enzymes were detected in various cell types, including pancreatic β-cells and insulin-responsive cells such as adipocytes. Adipose tissue is a major site of vitamin D storage and an important source of adipokines and cytokines participating in the formation of systemic inflammation. It is well known that obesity, especially visceral, is one of the major risk factors for T2DM (3). Vitamin D, a lipophilic compound, may be trapped in adipose tissue, resulting in serum deficiency (4). Vitamin D deficiency contributes to decreased insulin secretion in pancreatic β cells so that it can be associated with the onset of diabetes (3,5,6). Physical exercise is a strong stimulus for lipid mobilization from adipose tissue so that it can increase circulating vitamin D serum (7-9).

Treadmill is a type of aerobic exercise that has many advantages. This form of exercise resembles a natural walking feature driven by a motor or manual equipment involving a large group of lower leg muscles along with a rhythmic upper body muscle (10,11). On a treadmill workout, the speed component relates to the fast-twitch muscle fibers recruited where the fast-twitch muscle produces a higher and stronger contraction force than the slow-twitch muscle fibers, whereas the gradual inclination will also involve more muscles being recruited and works to maintain balance (11). Muscles that work will be more sensitive to insulin response than muscles that are resting. The more muscles involved, the greater the assimilation of glucose per unit of insulin during exercise. The binding of insulin to the increased receptor sites further allows for greater insulin-mediated glucose uptake (10).

This study aims to compare 25(OH)D levels and pancreatic β cell function before and after moderate-intensity treadmill with increased speed and gradual inclination in type 2 diabetic patients. We hypothesized that there would be a significant rise of 25(OH)D levels and HOMA B value after 4 weeks of training and also there were significant differences in 25(OH)D levels and HOMA B value between the two groups.

METHODS

Study design and inclusion criteria

The design of this study was a randomized pre- and post-test group. Twenty-two patients were recruited in the study. The subjects were divided into two groups: the exercise group and the control group. Inclusion criteria were male patients who have been treated with medication standard T2DM, age within 35–55 years old, and systolic blood pressure within 110-130 mmHg and also signed the informed consent form. Subjects with chronic conditions such as restrictive/obstructive respiratory tract disease, history of cardiac, kidney, thyroid, liver disease or cancer, had erythema, ulcers or gangrene in one or both legs, peripheral diabetic neuropathy, use of medications such as long-term steroids or those taking vitamin D supplements, neuromusculoskeletal disease, vestibular and proprioceptive disturbance, and a patient had a routine aerobic exercise at least two times per week were excluded from the study. Dropout criteria included changes of ischemia or cardiac disease during an exercise identified by electrocardiogram or if there were complaints of hypoglycemia, chest pain, or tightness during or after exercise. The study was approved by the Ethics committee of Dr. Soetomo General Academic Hospital Surabaya, Indonesia with ethical clearance no.1266/KEPK/VI/2019. All participants received written and verbal information regarding the nature and potential risks of the study and they were required to provide signed informed consent.

Protocols

Twenty patients took part in the study for four weeks. Participants were assessed for clinical and biochemistry. Subjects were examined in detail for recording weight, height, and body mass index (BMI). Serum insulin, fasting blood glucose, 25(OH)D, and HOMA B were calculated. All measurements were performed at the beginning and after 4 weeks of training. All the subjects in both groups were recommended to continue their previous routine medications. The subjects in the control group were also instructed to maintain their modification lifestyle until the end of the study.

An aerobic exercise program was conducted for 4 weeks (3 sessions/week, moderate intensity). The training protocol was taken from the Modified Bruce test with a total of 7 stages with increasing speed and inclination periodically every 3 minutes to reach the target heart rate (60 %-75 % maximum heart rate). Before and after exercises, we examined vital signs for blood pressure, heart rate, and oxygen saturation. We also had checked blood sugar using a glucometer (easy touch) and explained about the Borg scale. Subjects in the exercise group were allowed to exercise if blood glucose level 100-250 mg/dL. Treadmill EN-Mill® 2007 were used as walking exercise devices. We utilized Polar H10 heartbeat sensors for the heart rate, installed them to the participant's chest, and connected them through Bluetooth to smartphones (Figure 1). The treadmill exercise was about 30 min long. A 5-min warm-up was initiated before the exercise then we had core exercises which lasted for 20 min and a 5-min cool-down.

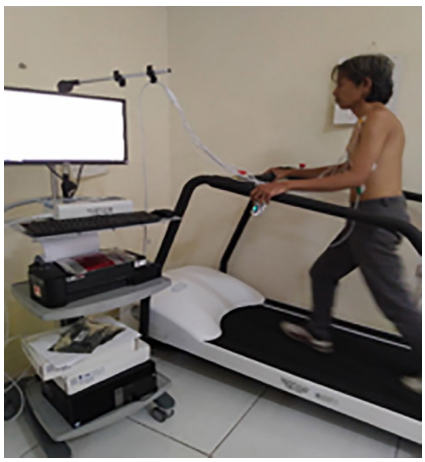

Figure 1. Participant in exercise group.

Blood samples were taken from all groups 30 min before the exercise and the last training program. Blood was drawn and put in a plain tube (without any activator) and kept in a -80 ºC refrigerator. 25(OH)D were measured using Siemens ADVIA Centaur Vitamin D with chemiluminescent immunoassay (CLIA). The function of pancreatic β cells was determined by homeostatic model assessment (HOMA) using fasting insulin and glucose concentrations. Homeostatic model assessment of β cell function (HOMA-B) was calculated through the formula: [(20 x fasting insulin (μU / mL)] / [(fasting blood sugar (mmol / L) -3.5)].

Data Analysis

We observe the average value of 25(OH)D and HOMA B. Statistical analysis was performed using SPSS for Windows version 26. The data were analyzed by descriptive tests such as mean, median, and SD (standard deviation). Shapiro-Wilk tests were performed to assess the normality of the variables before further statistical analysis. Delta 25(OH)D and HOMA B show the different values of pre-and post-exercise in each group. We used Independent samples test (for normally distributed) or Mann-Whitney U-Test (for non-normally distributed) to measure the significance of each group. The effects of treadmill exercise on the variables between the two groups were analyzed by Paired T-test (for normally distributed) or Wilcoxon test (for non-normally distributed). Statistical significance was set at $p<0.05$.

RESULTS

Twenty participants completed the 4-week intervention after two participants dropped out of the supported exercise due to hypoglycemia observed during the exercise tolerance test. All the participants were divided into two groups by randomized ballot. Table 1 demonstrates the descriptive statistics of the basic and clinical characteristics of the exercise and control groups. Patient characteristics at baseline were balanced between the two groups, especially for ages (p= 0.017). There were also no significant baseline differences between exercise and control groups for mean serum 25(OH) and HOMA-B levels.

Figure 2 shows the comparison of vitamin D status before and after treadmill exercise in the two groups. Before the program, the vitamin D status of the exercise group was 40 % for Vitamin D Insufficiency (VDI) and 60 % for Vitamin D Deficiency (VDD) while in the control group, they were 60 % for VDI and 40 % VDD. After the program, we got in the exercise group 10 % normal (Vitamin D sufficient), 60 % VDI, and 30 % VDD while in the control group, they were 20 % VDS, 50 % VDI, and 30 % VDD.

Figure 3 shows the change (delta) of vitamin D in the two groups. The mean delta 25(OH)D levels increase in the exercise group was 2.52 ± 4.65 ng/ml, while in the control group it also increased 1.53 ± 4.98 ng/mL. Comparison of delta 25(OH)D levels between two groups was calculated using the Mann Whitney test with the results of no statistically significant difference (P= 0.821).

Table 2 shows the comparison of vitamin D before and after the 4-week treadmill program in the two groups. Based on the Wilcoxon test, there was a significant difference in vitamin D levels before and after the treadmill exercise program in the exercise group (p= 0.041). Whereas in the control group, the paired T-test was used and there was no significant difference (p= 0.355) (Figure 4).

Figure 5 shows the change (delta) of HOMA-B in the two groups. The mean HOMA-B levels increase in the exercise group was 93.98±159.34 % and 227.7±284.08 % in the control group. Comparison of delta HOMA-B levels between two groups was calculated using the Mann Whitney test with the results of no statistically significant difference (p= 0.226). Table 3 shows baseline values and changes after 4 weeks in the two groups. HOMA-B level increased significantly in both groups as 197.77±245.6 % in exercise group (p = 0.013) and 343.38±349.86 % in control group (p = 0.032). There was a significant difference in the change of HOMA-B after 4-weeks in the exercise and control groups (Figure 6).

Table I

Descriptive characteristics

Basicp Characteristics	Exercise group (n=10)		Control groups (n=10)		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
Age (years)	50.7±4.52	51(40-55) **	46.10±3.84	47(40-52) **	0.017[b]
Duration of diabetes (years)	5.55±4.69	3(1.5-15) **	4.55±4.65	2(1-15) **	0.361[b]
BMI (kg/m^2)	23.89±3.56*	24.52(17.1-29.7)	26.66±4.44*	26.17(20.9-34.89)	0.141[a]
SBP (mmHg)	116±6.99	115(110-130)**	114±6.99	110(110-130) **	0.435[b]
HbA1C (%)	6.55±1.18*	6.35(4.5-9.0)	7.93±2.13*	7.7(5.2-11.8)	0.090[a]
Random blood glucose (mg/dL)	180.7±50.35*	178.5(103-280)	159.3±32.0*	152(117-228)	0.272[a]
25(OH)D (ng/mL)	19.22±4.06	18.3 (12.87-25.17) **	21.71±4.22	20.1 (17.38-29.59) **	0.226[b]
HOMA-B (%)	103.79±137.4	56.77 (13.3-456.8) **	115.68±127.8	63.00 (26.95-442.6) **	0.450[b]
Fasting Insulin (μU/mL)	11.28+6.17	10.22 (6.62-27.87) **	18.35+17.31	8.51 (5-24.85) **	0.545[b]
Clinical Characteristics	Σ	n (%)	Σ	n (%)	p
Insulin exogenous (%)	10	100	10	100	0.628[c]
Yes	4	40	2	20	
No	6	60	8	80	
Hypertension (%)	10	100	10	100	0.628[c]
Yes	4	40	2	20	
No	6	60	8	80	
Dyslipidemia (%)	10	100	10	100	1.000[c]
Yes	2	20	2	20	
No	8	80	8	80	

[a] = Independent T-test; [b] = Mann-Whitney test; [c] = Chi-Square test
Significant if p<0.05
Note. BMI: Body Mass Index; HOMA-B: Homeostatic model assessment of β cell function; SBP: Systolic Blood Pressure

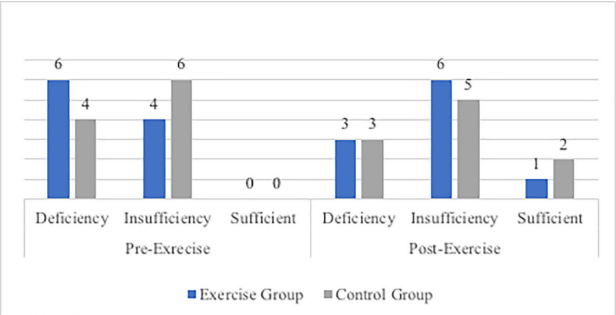

Figure 2. Clinical characteristics of vitamin D status in the two groups.

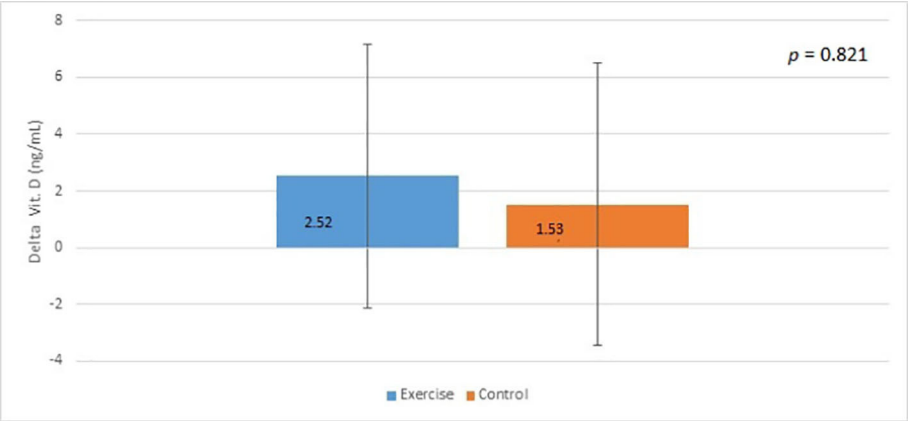

Figure 3. The change (Delta) of vitamin D in the two groups.

Table 2

Vitamin D levels before and after treadmill in both groups

Vitamin D	N	Mean ± SD (ng/mL)		p-value
		Pre	Post	
Exercise Group	10	19.22 ± 4.06	21.74 ± 4.53	0.041*
Control Group	10	21.71 ± 4.22	23.25 ± 5.46	0.355

* Significant if P <0.05

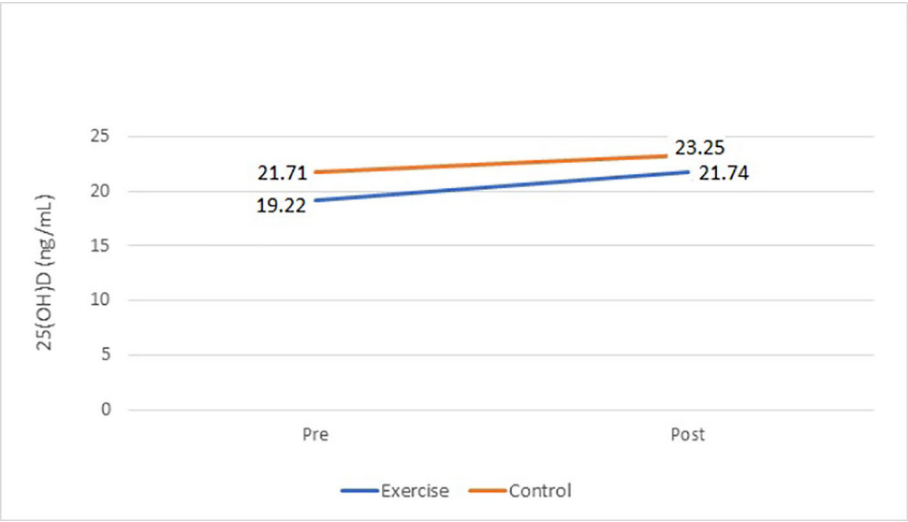

Figure 4. Changes in mean of 25(OH)D from baseline to week-4 in the two groups.

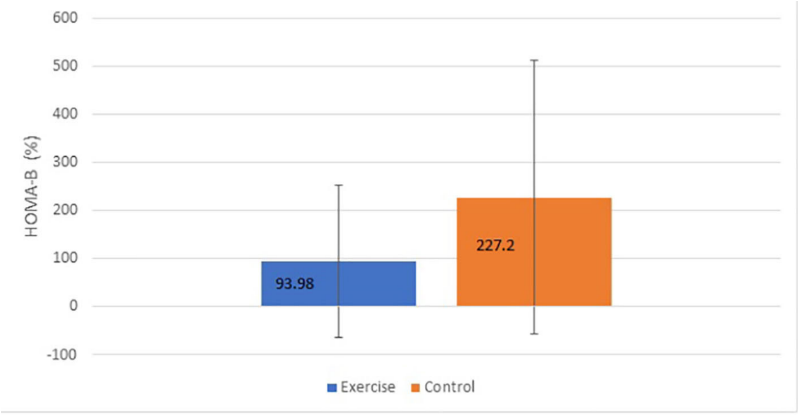

Figure 5. The change (Delta) of HOMA-B levels in the two groups.

Table 3

HOMA-B levels Before and After Treadmill in Both Groups

HOMA-B	N	Mean ± SD (%)		p-value
		Pre	Post	
Exercise Group	10	103.79 ± 137.49	197.77 ± 245.60	0.013*
Control Group	10	115.68 ± 127.89	343.38 ± 349.86	0.032*

* Significant if p <0.05

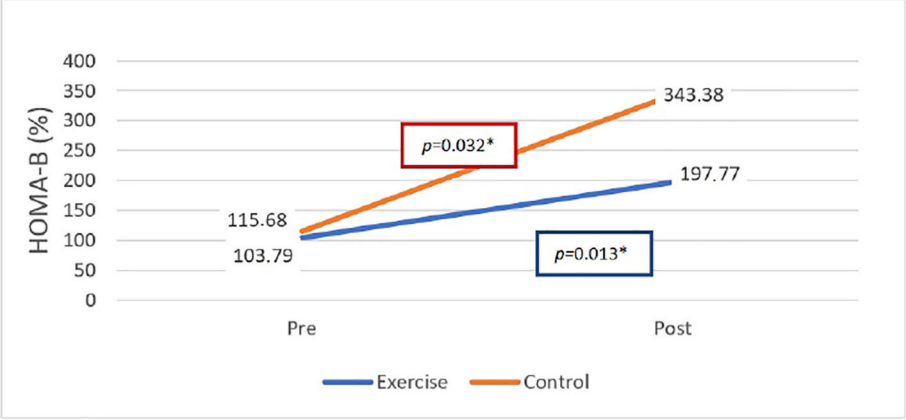

Figure 6. Changes in mean of HOMA-B from baseline to week-4 in the two groups.

DISCUSSION

Changes in vitamin D levels can occur in both groups because the intervention given to both groups, supervised and independent physical exercise, so that affected increasing vitamin D levels. The results of this study are in accordance with several previous studies which reported a positive relationship between physical exercise and vitamin D levels. In this study, there were a significant difference in the mean 25(OH)D levels before and after the treadmill exercise program in the exercise group. Meanwhile, in the

control group, there was no significant difference in 25(OH)D before and after the 4-week program. Previous research has also shown a positive relationship between physical activity and vitamin D levels. According to the studies analyzed, the increased plasma concentration of vitamin D occurs with physical activity both indoors and outdoors (12). A randomized trial study using a parallel-group design method conducted by Aoki et al. (2018) in Japan reported the change (delta) of vitamin D in the exercise group was 1.4 ± 2.33 ng/mL (p= 0.385) compared to the vitamin D group was 20.5 ± 2.42 ng/mL (p= 0.001). An intervention study on 22 subjects conducted by Sun et al. (2017) in Japan also proved that there was a direct effect of physical exercise on serum 25(OH)D concentrations, both acute and chronic exercise (9). Several other studies also reported the same thing that exercise could be a therapeutic target of adipose tissue dysfunction. Chronic increase in physical activity can increase adipocyte function so that regular physical exercise can increase sensitivity to various mediators such as insulin and adrenaline in adipose tissue in individuals with metabolic syndrome.

Several previous studies have been conducted to determine vitamin D status and its relationship with glycemic control in type 2 diabetes mellitus. In this study the subjects were given the intervention of physical activity, treadmill exercise, then analysis was carried out regarding changes in vitamin D levels before and after exercise. The level of vitamin D was serum 25(OH)D (calcidiol). Differences in vitamin D status were influenced by many other confounding factors such as age, race/ethnicity, ultraviolet exposure, gender, BMI, physical activity, use of drugs that affect vitamin D metabolism, and various comorbid diseases (12,13). Vitamin D status was also associated with cardiometabolic diseases such as metabolic syndrome, obesity, hypertension, and diabetes (3,6).

Vitamin D is lipophilic and accumulates substantially in adipose tissue. Treadmill exercise is a powerful stimulus for lipid mobilization from adipose tissue. It is therefore conceivable that vitamin D 'trapped' in adipocytes is mobilized (along with stored lipid) by physical activity. During exercise, there is a rise in plasma glucagon, adrenaline, and atrial natriuretic peptide (ANP) and a decrease in plasma insulin concomitant with increased adipose tissue blood flow. Glucagon, adrenaline, and ANP are stimulatory lipolytic hormones, and suppression of insulin leads to a potent increase in lipolysis. This leads to hydrolysis of triacylglycerol from the lipid droplet of adipocytes by the action of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). Exercise in the fasted or the fed state leads to an approximate twofold to threefold increase in adipose tissue lipolysis and, when stored triacylglycerol is hydrolyzed, vitamin D metabolites may also be released from the lipid droplet (7,8).

Insulin resistance and impaired β cell function are important pathological bases for impaired glucose metabolism and the occurrence of type 2 diabetes. According to a population-based study conducted by Cai et al., (2019) in China, insulin resistance is a major determinant of the development of prediabetes while cell function β is the main determinant of the development of type 2 diabetes (13). The subject population in this study were patients with type 2 diabetes, so changes in pancreatic β cell function after being given treadmill exercise intervention are important to evaluate. In this study, the mean value of HOMA-B in the exercise group was 103.79 ± 137.49 % and in the control group was 115.68 ± 127.89 %. This value indicates that the function of pancreatic β cells in both groups was still in the normal range (N: 70-150 %) and there was no significant difference between the two groups (p= 0.450). In this study, the mean value of HOMA B in the exercise group was lower than that of the control group possibly due to several associated risk factors present in the study subjects. In the exercise group, initial data were obtained that the duration of suffering from disease was longer than in the control group (5.5 years) compared to the control group, which was only 4.5 years (p= 0.361), so the possibility of a decrease in beta-cell function was greater in the exercise group. In addition, in the majority of subjects in the exercise group, comorbid hypertension was greater (40 %) compared to the control group (20 %) with mean systolic blood pressure in the exercise group which was also higher (116 ± 6.99 mmHg) compared with the control group (114 ± 6.99 mmHg).

The results of this study indicate that the

pancreatic beta-cell compensation appears heavier in the control group. HOMA-B which has exceeded 150 % means that there was excess activity of beta cells which leads to loss of beta-cell function. In this study, the results showed that there were significant differences in HOMA-B before and after the exercise program in the two groups, the exercise group, and the control group. This happens because of the effect of exercise on the body's metabolism, both acute and chronic. Treadmill with an increasing speed and gradual inclination will increase the body's metabolism, involve more muscles working rhythmically, increasing energy requirements so that the required oxygen consumption is also greater. Increasing the speed will gradually increase the heart rate along with the load speed. The higher the speed, the muscles will work harder so that oxygen demand also increases. This increase in oxygen demand as a source of energy to maintain performance in completing exercise duration (14). The gradual increase in inclination will also increase the work activity of the lower limb muscle groups. This increase in activity is due to increased muscle function in addition to moving as well as maintaining balance (15). Furthermore, the action of insulin on the muscles and liver can be modified by both the acute effect of exercise and regular physical activity so that a supervised exercise program can better improve glycemic control through increased β cell function (16).

CONCLUSION

Moderate intensity treadmill exercises with increased speed and gradual inclination can increase vitamin D levels and pancreatic β cell function.

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Disclosure

The authors declare no conflicts of interest.

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Malondialdehyde levels and clinical outcomes assessed by the modified Rankin scale in patients with acute intracerebral hemorrhagic stroke

Niveles de malondialdehído y resultados clínicos evaluados por la escala de Rankin modificada en pacientes con accidente cerebrovascular hemorrágico intracerebral agudo

Abdulloh Machin[1]•, Nurlisa Naila Aulia[2], Sita Setyowatie[3]

SUMMARY

Background: *Oxidative stress plays an important role in secondary brain injury after a stroke of intracerebral hemorrhage. This study aimed to determine the association between malondialdehyde (MDA) levels with clinical outcomes assessed using the modified Rankin Scale (mRS) in patients with acute intracerebral hemorrhagic stroke.*
Methods: *A cohort study was enrolled in patients with intracerebral hemorrhagic stroke in Dr. Soetomo General Hospital Surabaya, Indonesia. The study subjects were blood drawn for the examination of MDA levels at hospital admission, and the examination of clinical outcomes was assessed using the mRS when the patient was discharged from the hospital.*
Results: *In 34 study subjects, 23 subjects with poor mRS and 11 subjects with good mRS were obtained. The results of the study analysis showed that subjects who had MDA levels >494.95 ng/mL with poor mRS were 17 subjects (73.9 %), higher than those with good mRS, 3 subjects (27.3 %). There were not statistically significant differences between age, GCS, bleeding volume, and MDA with clinical outcomes (p>0.06). However, there was an association between MDA levels clinical outcomes with p = 0.023 and relative risk (RR) of 1.983 (95 % CI 1.054-3.732).*
Conclusion: *There was a significant association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke.*

Keywords: *Levels of malondialdehyde, modified Rankin Scale, cardiovascular disease.*

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RESUMEN

Antecedentes: *El estrés oxidativo juega un papel importante en la lesión cerebral secundaria después de un accidente cerebrovascular de hemorragia intracerebral. Este estudio tuvo como objetivo determinar la asociación entre los niveles de malondialdehído (MDA) y los resultados clínicos evaluados mediante la escala de Rankin modificada (mRS) en pacientes con accidente cerebrovascular hemorrágico intracerebral agudo.*
Métodos: *Se realizó un estudio de cohorte en pacientes con accidente cerebrovascular hemorrágico intracerebral en el Hospital General Dr. Soetomo de Surabaya, Indonesia. A los sujetos del estudio se les extrajo sangre para el examen de los niveles de MDA en el momento de la admisión al hospital, y el examen de los resultados clínicos se evaluó mediante la mRS cuando el paciente fue dado de alta del hospital.*
Resultados: *En 34 sujetos de estudio, se obtuvieron 23 sujetos con mRS pobre y 11 sujetos con mRS buena. Los resultados del análisis del estudio mostraron que 17 sujetos (73,9 %), presentaban niveles de MDA> 494,95 ng/mL con mRS pobre, y 3 sujetos (27,3 %) más altos que aquellos con mRS buena. No hubo diferencia estadísticamente significativa entre la edad, la GCS, el volumen de sangrado y la MDA con los resultados clínicos (p> 0,06). Sin embargo, hubo una asociación entre los resultados clínicos de los niveles de MDA con p= 0,023 y el riesgo relativo (RR) de 1,983 (IC del 95 %: 1,054-3,732).*
Conclusión: *Hubo una asociación significativa entre los niveles de MDA y los resultados clínicos evaluados mediante la mRS en pacientes con accidente cerebrovascular hemorrágico intracerebral agudo.*

Palabras clave: *Niveles de malondialdehído, escala de Rankin modificada, resultados clínicos.*

INTRODUCTION

Stroke is the second leading cause of death in the world and the highest cause of disability in the world, with intracerebral hemorrhagic strokes having an incidence of 10-20 cases per 100 000 population and reaching 10-15 % of all strokes worldwide each year (1,2). Indonesian stroke registry data in 2014 reported that the number of hemorrhagic strokes was 32.9 % of all strokes in Indonesia. The highest mortality rate was recorded in hemorrhagic stroke, which was 20.3 % after 48 hours and 18.3 % in less than 48 hours. This amount is higher than the mortality rate in ischemic stroke. As many as 52 % of patients die within the first month, and only 20 % will live independently within six months (3).

Compared with the same infarction size, intracerebral hemorrhage produces more inflammation and cell death. The pathophysiological process playing a role in inflammatory damage mediated by cellular and non-cellular components (4). Oxidative stress plays an important role in secondary brain injury after intracerebral hemorrhagic stroke because it causes permanent disruption in the cortex and subcortex components followed by impaired brain-blood barrier and brain edema with massive brain cell death (5). The lysis of red blood cells on the first day after intracerebral hemorrhagic stroke will release hemoglobin converted by the enzyme heme oxygenase-1 (HO-1) into neurotoxic components, such as heme and iron, that play a role in secondary brain injury (6). Early microglial activation, the release of pro-inflammatory mediators, and the influx of peripheral leukocytes will trigger neuroinflammation after intracerebral hemorrhagic stroke releasing large amounts of reactive oxygen species (ROS), causing excessive consumption of superoxide dismutase (SOD) and lipid peroxidation (5,6). Lipid hydroperoxide is the main product of the lipid peroxidation process. The structure of lipid hydroperoxides is very unstable and can easily change into malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), and several other forms of aldehyde. MDA is the main secondary product in the lipid peroxidation process because it is more mutagenic than other aldehydes (7). Currently, MDA is more often used in biomedical research as a marker of oxidative stress, especially in various clinical conditions related to the lipid peroxidation process. The chemically stable nature of MDA makes it more often used as a marker of oxidative stress compared to 4-HNE (8).

A previous study showed that MDA levels increased in patients with both acute hemorrhagic and ischemic strokes compared to healthy controls (9). Another study also stated that serum MDA levels were significantly higher in patients with intracerebral hemorrhagic stroke compared to healthy controls and in patients who did not survive compared to patients who

survived. Furthermore, serum MDA levels were associated with 30-day mortality (OR= 6.279; 95 % CI= 1.940-20.319; p= 0.002) (10).

Modified Rankin Scale (mRS) is used to assess functional limitations after stroke, including aspects of daily personal life, such as eating, toileting, bathing, walking, preparing meals, traveling, shopping and social life of work, family responsibilities, social activities, and entertainment. mRS is a global measurement tool with good reliability and validity. This study aimed to prove the association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke.

METHODS

The study design used in this study was a cohort. This study was conducted from August 2019 to November 2019 in Dr. Soetomo General Hospital, Surabaya. The inclusion criteria were patients aged 20 years and over, patients with the first attack of acute intracerebral hemorrhagic stroke that has been done clinical examination and head CT scan without contrast, patients' onset 24-72 hours, and patients who were willing to follow the study. Meanwhile, the exclusion criteria of this study were patients with acute intracerebral hemorrhagic stroke accompanied by intraventricular or subarachnoid hemorrhage, having an infection at the time of hospital admission, diabetes mellitus, acute coronary heart disease, history of malignancy, and Parkinson's disease.

The sample size was determined by the sample size formula for the unpaired categorical analytic study, the two-way hypothesis with a type I error of 5 %, and a type II error of 20 %. The value of the proportion of effects in groups with risk factors (P1) and groups without risk factors (P2) was determined based on a previous study, and the minimum sample size was 17 people for each group so that the sample size was 34 people. If a minimum of 10 % dropout was added, the total sample size was 38 people. The sampling method was conducted according to consecutive cases (sampling on consecutive admission) until a predetermined number of samples has been reached. There were 40 study subjects. Six subjects were dropped out of the study because of an infection during hospitalization in 2 subjects and blood lysis when storing in 4 subjects so that 34 (thirty-four) study subjects were collected.

The study subjects were blood drawn for examination of malondialdehyde levels at hospital admission and examination of clinical outcomes assessed using the mRs carried out when the patient was discharged from the hospital. Statistical analysis was performed with SPSS 21. The results of the study were analyzed using Chi-Square statistical tests, and Relative Risk (RR) calculations were performed.

RESULTS

Demographic data of study subjects, including age, sex, length of education, level of education, occupation, marital status, and ethnicity, can be seen in Table 1. Demographic characteristics include sex and age.

Table 1

Demographic characteristics of subjects

Variables	N (%)	Mean±SD
Sex		
Male	20 (58.8)	
Female	14 (41.2)	
Age		57.32±12.51
>75 years old	3 (8.8)	
≤75 years old	31 (91.2)	

Clinical characteristics include hypertension, smoking, location of stroke lesions, bleeding volume, GCS, MDA levels, and mRS. The clinical characteristics of study subjects can be seen in Table 2.

Table 2

Clinical characteristics of study subjects

Variables	N (%)	Mean±SD
Hypertension		
Grade I	12 (35.3)	
Grade II	22 (64.7)	
Smoking		
Yes	8 (23.5)	
No	26 (76.5)	
Location of Stroke lesions		
Right	16 (47.1)	
Left	18 (52.9)	
Bleeding Volume		16.41±12.30
<30 cc	30 (88.2)	
≥30 cc	4 (11.8)	
GCS		
Good (13-15)	23 (67.6)	
Poor (<13)	11 (32.4)	
MDA levels		1136.50±1042.78
<494.95	14 (41.2)	
>494.95	20 (58.8)	
mRS		
Good	11 (32.4)	
Poor	23 (67.6)	

MDA: malondialdehyde; mRS: Modified Rankin Scale

The results of the analysis of the association between age, GCS, bleeding volume, and MDA with clinical outcomes can be seen in Table 3. There was no statistically significant between age, GCS, bleeding volume, and MDA with clinical outcomes (p>0.06). However, there was an association between MDA levels clinical outcomes with p= 0.023 and relative risk (RR) of 1.983 (95 % CI 1.054-3.732).

DISCUSSION

The results of the analysis of the association between MDA levels and clinical outcomes assessed using mRS showed statistically significant results. The subjects with high MDA levels >494.950 ng/mL had a 1.9 times higher risk of experiencing poor clinical outcomes of mRS compared to subjects who had low MDA levels <494.950 ng/mL. The results of this study are in accordance with a recent study showing that high MDA levels were associated with 30-day mortality with a p value=0.002 and an odds ratio value of 6.279 (95 % CI, 1.940-20.319) (10).

Table 3

The result of correlation test

Variables	mRS		Total	p
	Poor	Good		
Age				0.53
Age ≥ 75 y.o.	3 (13.0 %)	0 (0.0 %)	3	
Age < 75 y.o.	20 (87.0 %)	11 (100 %)	31	
GCS				1.000
Poor GCS (<13)	8 (34.8 %)	3 (27.3 %)	11	
Good GCS (13-15)	15 (65.2 %)	8 (72.7 %)	23	
Bleeding Volume				1.000
Volume ≥30cc	3 (13.0 %)	1 (9.1 %)	4	
Volume <30cc	20 (87.0 %)	10 (90.9 %)	30	
MDA				0.023
High MDA >494.95 ng/mL	17 (73.9 %)	3 (27.3 %)	20	
Low MDA <494.95 ng/mL	6 (26.1 %)	8 (72.7 %)	14	

MDA: malondialdehyde; mRS: Modified Rankin Scale

The basic characteristics of the study subjects include demographic characteristics and clinical data. Demographic characteristics include age and sex. Based on demographic data, most of the study subjects aged <75 years and were male. The results of the analysis for the association between confounding variables and clinical outcomes assessed using the mRS in this study showed no statistically significant differences for age, initial GCS, and bleeding volume variables.

In this study, we found that subjects who were >75 years old with poor mRS did not have a statistically significant difference when compared with subjects who were >75 years old with good mRS. This result differs from previous studies which stated that older age had poor mRS values (11). This difference in results could be due to the fact that in this study, most of the subjects had an age of <75 years. In addition, subjects who at the time of initial hospital admission had decreased consciousness with GCS <13 with poor mRS did not have a statistically significant difference when compared to subjects who at the time of initial hospital admission had decreased consciousness with GCS <13 with good mRS. These results are different from previous studies stating that subjects who entered with poor initial GCS had poor mRS outcomes (12). The difference in these results could be due to the fact that in this study, the majority of subjects at hospital admission had a good initial GCS.

In this study, subjects with bleeding volume ≥30 cc with poor mRS did not have a statistically significant difference compared to subjects with bleeding volume ≥30 cc with good mRS. These results are different from previous studies stating that bleeding volume ≥30 cc had poor mRS outcome (12). This difference in results could be caused by most subjects having a bleeding volume of <30 cc.

MDA levels increase in patients with both acute hemorrhagic and ischemic strokes compared to healthy controls (9). These findings are consistent with several previous studies that examined levels of oxidative stress using MDA and Total Antioxidant Capacity (TAC) in 24 hemorrhagic stroke patients and 24 ischemic stroke patients confirmed by head CT-Scan associated to awareness level and the National Institutes of Health Stroke Scale (NIHSS) in ischemic stroke, as well as the location and volume of the hematoma in hemorrhagic stroke. A significant positive correlation was obtained between MDA levels and bleeding volume in hemorrhagic stroke patients and a negative correlation between TAC levels and bleeding volume (13). This is different from another study that compared levels of Total Oxidant Status (TOS), Total Antioxidant Status (TAS), and MDA in patients with intracerebral hemorrhagic strokes with healthy controls. Compared to the control group, TOS, TAS, and MDA levels were significantly higher in patients with intracerebral hemorrhagic stroke. However, there was no correlation between TOS, TAS, and MDA levels with the Glasgow Coma Scale (GCS) total score and hematoma volume (14).

MDA is the main secondary product in the lipid peroxidation process often used as a marker of oxidative stress because it has a more stable chemical compound. Oxidative stress is involved not only in pathological processes but also at various important stages in the pathophysiological response during intracerebral hemorrhage, including causing brain cell death. Brain cell death will result in impairment of function and ADL that can be assessed with the mRS.

This study has advantages. This is the first study conducted in Indonesia, especially in Surabaya, focusing on the association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke in Dr. Soetomo General Hospital, Surabaya. The limitation of this study is that this study was only conducted in one hospital and based on hospital data so that it cannot be generalized to the population. In addition, the mRS assessment was only done when the patient was discharged from the hospital regardless of the length of time of treatment.

CONCLUSION

There was a significant association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke in Dr. Soetomo General Hospital, Surabaya.

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Association between bleeding volume with heme oxygenase-1 and malondialdehyde levels in patients of acute intracerebral hemorrhage

Asociación entre el volumen de sangrado con la hemo oxigenasa-1 y los niveles de malondialdehído en pacientes con hemorragia intracerebral aguda

Sita Setyowatie[1], Abdulloh Machin[2]•, Nurlisa Naila Aulia[3]

SUMMARY

Background: *Oxidative stress plays an important role in secondary brain damage after a stroke of intracerebral hemorrhage because it causes permanent damage to grey matter, white matter taken by brain blood barrier disorders, and brain edema with brain cells. This study aimed to determine the correlation between bleeding volume and heme oxygenase-1 (HO-1) and malondialdehyde (MDA) levels in stroke patients with acute intracerebral hemorrhage at Dr. Soetomo Hospital, Surabaya.*

Methods: *This was a cross-sectional analytic study with 34 study subjects who met the inclusion and exclusion criteria from August 2019 to November 2019. Subjects were measured for bleeding volume and blood collection for examination of HO-1 levels and MDA levels at hospital admission in stroke patients with acute intracerebral hemorrhage.*
Results: *The mean bleeding volume in this study was 15.34±10.26 mL, the mean level of HO-1 was 55.51±138.06 ng/mL, and the mean level of MDA was 1066.03±907.97 ng/mL. Statistical analysis did not obtain any significant correlation between bleeding volume and HO-1 level (p= 0.605). However, there was a significant correlation statistically between bleeding volume and MDA level (r= 0.509; p= 0.002).*
Conclusion: *There was a correlation between bleeding volume level and the level of MDA in stroke patients with acute intracerebral hemorrhage, although there was no significant correlation between bleeding volume and HO-1 levels.*

Keywords: *Intracerebral hemorrhage stroke, heme oxygenase 1, malondialdehyde, oxidative stress, lipid peroxidation*

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RESUMEN

Antecedentes: *El estrés oxidativo juega un papel importante en el daño cerebral secundario después de un accidente cerebrovascular con hemorragia intracerebral porque causa daño permanente a la sustancia gris, sustancia blanca blanca tomada*

por los trastornos de la barrera hematoencefálica y edema cerebral con las células cerebrales. Este estudio tuvo como objetivo determinar la correlación entre el volumen de sangrado y los niveles de hemo oxigenasa-1 (HO-1) y malondialdehído (MDA) en pacientes con accidente cerebrovascular con hemorragia intracerebral aguda en el Hospital Dr. Soetomo, Surabaya.

Métodos: *Este fue un estudio analítico transversal con 34 sujetos que cumplieron con los criterios de inclusión y exclusión, desde agosto de 2019 hasta noviembre de 2019. Se midió el volumen de sangrado y se recolectó sangre de los sujetos para examinar los niveles de HO-1 y los niveles de MDA, al ingreso hospitalario en pacientes con accidente cerebrovascular con hemorragia intracerebral aguda.*

Resultados: *El volumen de sangrado medio en este estudio fue de 15,34 ± 10,26 mL, el nivel medio de HO-1 fue de 55,51 ± 138,06 ng/mL y el nivel medio de MDA fue de 1 066,03 ± 907,97 ng/mL. El análisis estadístico no obtuvo ninguna correlación significativa entre el volumen de sangrado y el nivel de HO-1 (p= 0,605). Sin embargo, hubo una correlación estadísticamente significativa entre el volumen de sangrado y el nivel de MDA (r= 0,509; p= 0,002).*

Conclusión: *Hubo una correlación entre el volumen de sangrado y el nivel de MDA en pacientes con ictus con hemorragia intracerebral aguda, aunque no hubo una correlación significativa entre el volumen de sangrado y los niveles de HO-1.*

Palabras clave: *Ictus hemorragia intracerebral, hemo oxigenasa-1, malondialdehído, estrés oxidativo, peroxidación lipídica.*

INTRODUCTION

Stroke is the second leading cause of death in the world and the highest cause of disability in the world, with intracerebral hemorrhage strokes having an incidence of 10-20 cases per 100 000 population and an estimated 10-15 of all strokes worldwide each year (1,2). Indonesian stroke registry data in 2014 reported that the number of hemorrhage strokes was 32.9 % of all strokes in Indonesia. The highest mortality recorded in hemorrhage strokes is equal to 20.3 % after 48 hours and 18.3 % less than 48 hours, greater than the mortality rate in infarct stroke. 52 % of patients died within the first month and only 20 % lived independently within 6 months (3).

In an intracerebral hemorrhage stroke, it will form a hematoma that can damage the anatomical structure of the brain, causing a neurological deficit and the effect of the urgency of space that can cause an increase in intracranial pressure. Hematoma volume >30 mL is associated with increased mortality due to intracerebral hemorrhage stroke, with mortality rates that increase to >90 % in hematoma volumes >60 mL (4). Hematoma expansion and perihematomal edema result in secondary brain injury and worsen clinical outcomes (4,5).

The interactions between cytotoxicity, excitotoxicity, oxidative stress, and lysis product inflammation from red blood cells and plasma components are the cause of secondary brain injury after intracerebral hemorrhage stroke (6). Lysis of red blood cells in the hematoma will release hemoglobin which is converted by the enzyme heme oxygenase-1 (HO-1) into neurotoxic components, heme, and iron which play a role in secondary brain injury through the induction of oxidative stress by HO-1 activation and iron-related free radicals through the Fenton reaction (7). The early activation of microglia, the release of proinflammatory mediators, and the influx of peripheral leukocytes will trigger neuroinflammation after intracerebral hemorrhage stroke that releases large amounts of reactive oxygen species and lipid peroxidation (5,7). Lipid hydroperoxide is the main product of the lipid peroxidation process. The structure of lipid hydroperoxide is very unstable and can easily turn into malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), and several other forms of aldehyde. MDA is the main secondary product in the lipid peroxidation process because it is more mutagenic than other aldehydes (8). This compound was first used in 1950 as a sign of damage to food. Currently, MDA is more often used in biomedical research as a marker of oxidative stress, especially in various clinical conditions related to the lipid peroxidation process. The chemically stable nature of MDA makes it more often used as a marker of oxidative stress compared to 4-HNE (9).

Research on intracerebral hemorrhage stroke and its relation to oxidative stress has not been conducted in Indonesia and has never been performed in Dr. Soetomo Hospital, Surabaya. This study aims to determine the volume of bleeding with levels of HO-1 and MDA as a

marker of oxidative stress in stroke patients with acute intracerebral hemorrhage.

METHODS

Subjects

This was a cross-sectional observational analytic study aiming to determine the correlation between bleeding volume with HO-1 and MDA levels. The study was conducted at Dr. Soetomo Hospital, Surabaya, Indonesia, from August to November 2019. The study population was intracerebral hemorrhage stroke patients who came for treatment at Dr. Soetomo Hospital, Surabaya. The study sample was all hemorrhage stroke patients who came for treatment and met the criteria for sample acceptance. Criteria for acceptance of the sample were stroke patients with the first acute intracerebral hemorrhage who had clinical examinations and head CT scans without contrasting the onset of stroke between 24-72 hours, aged ≥20 years, were willing to participate in the study, and signed informed consent. Criteria for rejection of the sample were stroke patients with acute intracerebral hemorrhage accompanied by intraventricular hemorrhage or subarachnoid hemorrhage, having an infection upon hospital admission, suffering from diabetes mellitus, acute coronary heart disease, Parkinson's disease, and a history of malignancy. The sampling technique was conducted by consecutive sampling by taking research subjects who meet the criteria for receiving samples sequentially until the desired sample size was met. The total sample of the study was 34 patients.

Methods

Bleeding volume was measured from digital CT images with the ABC/2 formula described by Broderick (A: the largest bleeding diameter by CT, B: Diameter 90 to A, and C: estimated number of CT slices with bleeding multiplied by slice thickness).

Blood samples were centrifuged at 4°C at a speed of 3 000 rpm for 10 minutes; and after the serum was separated, it was stored at -80°C until analysis. HO-1 and MDA levels were measured by the Enzym-linked immunosorbent assay (ELISA) technique.

Data analysis

Data obtained from the data collection sheet were analyzed. Data analysis was performed using the Statistical Package for Social Science (SPSS) version 21.0 program with a statistical significance of $p<0.05$. The correlation between bleeding volume with HO-1 and MDA levels in stroke patients with acute intracerebral hemorrhage was analyzed by Spearman rank correlation tests.

RESULTS

Demographic characteristics based on age obtained that the youngest age of patients with intracerebral hemorrhage stroke in this study was 40 years, and the oldest was 87 years, with an average age of study 60.74±13.10 years. Based on the sex, there were 22 (64.7 %) male subjects and 12 (35.3 %) female subjects.

Clinical characteristics of the study subjects included hypertension, smoking, bleeding volume, HO-1 levels, and MDA levels. In this study, 26 subjects (76.5 %) had hypertension, and 8 subjects (23.5 %) did not suffer from hypertension. Patients with a history of smoking were 8 subjects (23.5 %), and the non-smokers were 26 subjects (76.5 %). In this study, the minimum value of bleeding volume was 0.5 mL, and the maximum value of bleeding volume was 37.40 mL, with the mean value of bleeding volume being 15.34±10.26 mL. At the level of HO-1, the minimum value was 0.08 ng/ml, and the maximum value was 816.00 ng/ml, with the mean value of HO-1 being 55.51±138.06 ng/ml. The level of MDA obtained a minimum value of 202.50 ng/mL and the maximum value of 3173 ng/mL, with an average value of MDA levels of 1066.03±907.97 ng/mL. The characteristics of study subjects, including demographic and clinical data, are summarized in Table 1.

The mean value of HO-1 levels in study

Table 1

Characteristics of study subjects

Variable	n	Percentage (%)	Mean±SD
Age (years)			60.74±13.10
Sex			
Male	22	64.7	
Female	12	35.3	
Hypertension			
Yes	26	76.5	
No	8	23.5	
Smoking			
Yes	8	23.5	
No	26	76.5	
Bleeding volume (cc)			15.34±10.26
HO-1 levels (ng/mL)			55.51±138.06
MDA levels (ng/mL)			1066.03±907.97

HO-1: Heme oxygenase-1; MDA: Malondialdehyde

subjects who smoked was 23.31±16.37 ng/mL, while the mean value of HO-1 levels in non-smoking study subjects was 65.42±157.01 ng/mL. Based on statistical analysis, there was no difference in the levels of HO-1 in the smoking and non-smoking groups with p= 0.569. The mean value of MDA levels in smoking subjects was 1283.78±952.89 ng/ml, while the mean value of MDA in non-smoking research subjects was 999.03±902.30 ng/mL. Based on statistical analysis, there were no differences in the levels of MDA in the smoking and non-smoking groups (p= 0.503).

The results of the correlation analysis between age and HO-1 levels found a statistically significant correlation between age and HO-1 levels with p= 0.043. The results of the correlation analysis between age and MDA levels found no statistically significant correlation between age with MDA heme levels with a value of p= 0.613.

In this study, the normality test was first performed on the variable bleeding volume with levels of HO-1 and MDA with the Kolmogorov-Smirnov test. From the analysis, it was found that the bleeding volume variable has a normal data distribution, but the variable HO-1 and MDA levels had an abnormal data distribution. Hence, the next analysis was performed using the spearman rank correlation. The results of this study did not find a statistically significant correlation between the volume of bleeding with HO-1 levels with a value of p= 0.605, but there was a positive correlation between the volume of bleeding with levels of MDA and statistically significant correlation with values of p= 0.002 and r= 0.509.

DISCUSSION

Our finding showed that there was a significant positive correlation between the bleeding volume with MDA levels. The results of this study are consistent with an earlier study examining the levels of oxidative stress using MDA and Total Antioxidant Capacity (TAC) in 24 bleeding stroke patients and 24 ischemic stroke patients confirmed by CT head scan associated with the level of consciousness and National Institutes of Health Stroke Scale (NIHSS) in infarction strokes, as well as the location and volume of the hematoma in bleeding strokes. In hemorrhage stroke patients, a strong positive association has been established between MDA levels and bleeding volume, and a negative correlation between TAC levels and bleeding volume (10). This finding is consistent with several reports. MDA levels increased in patients with both bleeding and acute ischemic strokes compared to controls in healthy people (11). This is different from a previous study that compared the levels of Total Oxidant Status (TOS), Total Antioxidant Status (TAS), and MDA in intracerebral hemorrhage stroke patients with healthy controls. The TOS, TAS, and MDA levels in intracerebral hemorrhage stroke were substantially higher than in the control group. Nevertheless, the Glasgow Coma Scale (GCS) total value and the volume of hematoma were not correlated between TOS, TAS, and MDA (12).

Several factors affecting levels of HO-1 and MDA include age and smoking activity. In this study, the results of the analysis of the correlation between smoking and HO-1 levels were not statistically significant. These results are different from studies in experimental animals which reported that the expression of HO-1 in the carotid arteries of rats that smoked was much higher than in normal rats. HO-1 levels can protect vascular cells from oxidative stress induced

by cigarette smoke by reducing endogenous ROS (13). Similarly, the results of the analysis for the correlation of smoking with MDA levels were not statistically significant. This result is different from another study which stated that smoking significantly increased levels of MDA with a value of p= 0.001 (14). This difference in results can be caused because in this study most of the study subjects did not smoke (76.5 %).

The results of the analysis of age variables with HO-1 levels were statistically significant. This is in accordance with a research in 2003 stating that there is a significant positive correlation between age and HO-1 levels with r= 0.894 and p= <0.01 (15). The results of the analysis of age variables with MDA levels were not statistically significant with a p-value of 0.613. Thus, age was not a confounding factor for MDA levels although these results differed from other studies which stated that age >50 years had MDA levels higher than age ≤49 years (16).

The results of the analysis of the correlation between bleeding volume with HO-1 levels were not statistically significant. The results of this study differ from studies in 2015 stating that levels of HO-1 increase in stroke patients with intracerebral hemorrhage compared with healthy people (p= <0.001) (17). Extracellular heme is derived from hemoglobin after bleeding or released from damaged cells induces the expression of HO-1 which metabolizes heme to carbon monoxide, iron, and biliverdin. Immunohistochemical studies showed that the HO-1 protein was highly detected in the peri-ICH region, especially in microglia/macrophages and endothelial cells after ICH (18).

This study has advantages. This is the first study conducted in Indonesia, especially in Surabaya, about the correlation between bleeding volume and levels of HO-1 and MDA in stroke patients with acute intracerebral hemorrhage in Dr. Soetomo Hospital Surabaya. The limitation of this study is the small number of study subjects because this study was only conducted in one hospital and many confounding factors, such as age and smoking activity that can bias the results of the study.

CONCLUSION

There was a significant correlation between the level of bleeding volume with the level of MDA in stroke patients with acute intracerebral hemorrhage in Dr. Soetomo Hospital, Surabaya, although there was no significant correlation between bleeding volume and HO-1 levels.

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Triple elimination in pregnant women in Indonesia

Eliminación triple en mujeres embarazadas en indonesia

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SUMMARY

Background: *Triple elimination, which is an activity to control the transmission of Human immunodeficiency virus (HIV), syphilis, and hepatitis B from pregnant women to babies in Indonesia, has very minimal data regarding progress and current conditions. This study aims to identify the Triple Elimination profile at community health centers in Putat Jaya, Dupak, and Perak Timur, Surabaya.*
Methods: *This was a retrospective descriptive study by observing and examining medical record data of 1655 pregnant women who visited Antenatal Care (ANC) between January-December 2018.*
Results: *There were 1 655 data of pregnant women involved in this study. The coverage of antenatal care activities and quality complete early detection had test coverage results ≥95 %, completeness of tests >60 %, and results <0.30 %, <1.70 %, 7.10 % for HIV, syphilis, and hepatitis B, respectively, in three community health centers. In 2018, 3 cases of HIV, 4 cases of syphilis, and 41 cases of hepatitis B were found in three community health centers. The coverage of handling activities for positive pregnant women and childbirth has a 100 % percentage at Putat Jaya and Perak Timur Community Health Centers, but the data were incomplete at Dupak Community Health Center. No data were obtained regarding the coverage of children's examination activities and the handling of children from infected mothers.*
Conclusion: *The triple elimination program has met the criteria per the guidelines set by the World Health Organization. There were no pregnant women who*

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suffer from more than one disease from the three infectious diseases.

Keywords: *Triple elimination, pregnancy, HIV, syphilis, hepatitis B, profile*

RESUMEN

Antecedentes: *La Triple Eliminación, que es una actividad para controlar la transmisión del virus de la inmunodeficiencia humana (VIH), la sífilis y la hepatitis B de mujeres embarazadas a bebés en Indonesia, tiene muy pocos datos acerca del progreso y las condiciones actuales. Este estudio tiene como objetivo identificar el perfil de Triple Eliminación en los centros de salud comunitarios en Putat Jaya, Dupak y Perak Timur, Surabaya.*
Métodos: *Se trata de un estudio descriptivo retrospectivo mediante la observación y el examen de los datos de las historias clínicas de 1 655 mujeres embarazadas que visitaron la Atención Prenatal (ANC) entre enero y diciembre de 2018.*
Resultados: *Hubo 1 655 datos de mujeres embarazadas involucradas en este estudio. La cobertura de las actividades de atención prenatal y la detección temprana completa de calidad tuvieron resultados de cobertura de pruebas ≥95 %, completitud de las pruebas > 60 % y resultados <0,30 %, <1,70 %, 7,10 % para VIH, sífilis y hepatitis B, respectivamente, en tres centros de salud comunitarios. En 2018, se encontraron 3 casos de VIH, 4 casos de sífilis y 41 casos de hepatitis B en tres centros de salud comunitarios. La cobertura de las actividades para el manejo de mujeres embarazadas positivas y el parto tiene un porcentaje del 100 % en los Centros de Salud Comunitarios de Putat Jaya y Perak Timur, pero los datos estaban incompletos en el Centro de Salud Comunitario de Dupak. No se obtuvieron datos sobre la cobertura de las actividades de examen de los niños y el manejo de los niños de madres infectadas.*
Conclusión: *El programa de triple eliminación ha cumplido con los criterios establecidos por la Organización Mundial de la Salud. No hubo mujeres embarazadas que padecieran más de una enfermedad de las tres enfermedades infecciosas.*

Palabras clave: *Triple eliminación, embarazo, VIH, sífilis, hepatitis B, perfil.*

Abbreviations: HIV- Human immunodeficiency virus, STis - Sexually Transmitted Infections, WHO - World Health Organization, ANC - Antenatal Care MSM - Minimum Service Standards, EMTCT - Elimination Mother to Child Transmission, PPIA - Pencegahan Penularan dari Ibu ke Anak, HCV - Hepatitis C Virus, MTCT - Mother to Child Transmission, PMTCT - Prevention of Mother to Child-Transmission, HBV - Hepatitis B Virus, MSM - Men Sex with Men, FSW - Female Sex Workers, IDU - Injections Drug User

INTRODUCTION

Human immunodeficiency virus (HIV), syphilis, and hepatitis B are sexually transmitted infections (STIs) that can be transmitted by pregnant women to their babies. All three have the same transmission route in the form of sexual, blood, and vertical contact from mother to fetus. Vertical transmission of transmission from mother to fetus generally occurs during pregnancy, although it can occur during labor and breastfeeding at a lower frequency. Transmission of HIV, syphilis, and Hepatitis B to children from mothers has an impact on morbidity, disability, and death (1).

According to WHO data, in Southeast Asia in 2015, the HIV figure reached 5.1 million patients with 77 000 pregnant women living with HIV, and 19 000 new cases of pediatric HIV infection have been discovered. This figure is arguably fantastic compared to other regions. Meanwhile, for syphilis, the incidence rate has shown an increase of 0.32 % in Southeast Asia. The number of patients shows up to 167 000 cases of syphilis in pregnant women. It has a devastating effect, producing 65 800 adverse outcomes, including premature fetal death. For hepatitis B, Southeast Asia accounts for 15 % of the total number of hepatitis B patients worldwide with 39 million people.

In Indonesia, the prevalence rate for the three diseases reaches 0.39 % for HIV, 1.7 % for syphilis, and 2.5 % for hepatitis B (2). With a large population of Indonesia, this figure is still high. Thus, more attention is needed to overcome it. East Java, with five other provinces in Indonesia, i.e., West Java, DKI Jakarta, Riau, Bali, and Papua, is among the provinces considered HIV concentrated, indicating areas with high risk. The number of infections in East Java in 2017 was 39 633 infections. Surabaya is a contributor to a large number of patients. In 2017, 205 female

patients were found in Surabaya. However, this figure is still lower than expected because many cases are under-reported. The number of syphilis patients in Surabaya in 2017 was 126 people with 30 female patients. Hepatitis B in East Java has also shown a 3-fold increase in incidence in 2017. One thousand two hundred and eighty-seven cases have been reported with 80.4 % female patients or 1 035 patients (3). From the data listed above, a high number of female patients tends to increase the chance of infection. HIV, syphilis, and hepatitis B from mother to baby.

Prevention activities have been carried out by the Ministry of Health of the Republic of Indonesia with the implementation of a program called Triple Elimination per WHO recommendations (2017). These activities include the implementation of HIV, Hepatitis B, and Syphilis tests during Antenatal Care (ANC) for Pregnant Women. The Triple Elimination Program has a target of reaching zero by 2030 according to what is written in the Regulation of the Minister of Health of the Republic of Indonesia number 52 of 2017 concerning the Elimination of Transmission of HIV, Syphilis, and Hepatitis from Mother to Child. East Java Health Office 2017 data shows that 38 cities, including Surabaya, are still lacking ANC coverage for pregnant women, which should be 100 % in the Minimum Service Standards (MSS).

Research on STIs of HIV, syphilis, and hepatitis B in pregnant women, especially regarding the triple elimination program, is still very minimal. Previous research that was carried out was limited to the previous program, PPIA (4,5). In other countries, to be precise in the Netherlands, research was carried out (6). The results suggest that the number of HIV, syphilis, and hepatitis B infections is so low that it suggests WHO to re-validate the elimination program because more data is needed in its implementation. Several recent studies focusing on the profile of the triple elimination program have been carried out by several researchers abroad with much valuable information regarding the ongoing triple elimination (7,8). During its implementation to date in Indonesia, there is very little data on progress and current conditions. This is about the Triple Elimination program so that research needs to be done to evaluate whether the activities carried out are by the targets, targets, and scope of activities that have been set. Also, data on pregnant women who suffer from the three diseases in the form of HIV, syphilis, and hepatitis B are very minimal. In connection with this problem, this study aims to identify the Triple Elimination profile at community health centers in Putat Jaya, Dupak, and Perak Timur, Surabaya, Indonesia.

MATERIALS AND METHODS

This research is a type of retrospective descriptive study using total sampling by looking at and examining the medical records of 1 655 pregnant women who visited ANC (Antenatal Care). The research was conducted in three community health centers, Putat Jaya Community Health Center, Dupak Community Health Center, and Perak Timur Community Health Center. The selection of the three health centers was based on the estimation of the highest number of cases and the locations that were far apart representing all regions. Data collection was carried out from October to December 2019 at three community health centers. The inclusion criteria in this study were pregnant women who visited antenatal care to the community health centers in Putat Jaya, Dupak, and Perak Timur, Surabaya, while there were no exclusion criteria in this study. After getting the data through medical records, the data is then matched with the data recapitulation of the community health centers. Furthermore, the data were processed according to predetermined variables: 1) the test coverage which was divided into tested and not tested; 2) the completeness of the test with only 1 test, 2 tests, and complete categories; 3) the test results were only HIV positive, hepatitis only positive, syphilis positive only, HIV and syphilis positive, HIV and hepatitis positive, syphilis and hepatitis positive, all three HIV positive; 4) treatment of positive pregnant women divided into getting therapy, not getting therapy; 5) delivery place with the category of midwives, health centers, hospitals, and outside health facilities; 6) the treatment of infected infants is divided into receiving treatment and not receiving treatment; and 7) the results of the baby's test are HIV positive, syphilis positive, hepatitis B positive, negative. The first data

processing using Microsoft Excel. The data that has been collected is then analyzed using SPSS to get the desired results. Ethical clearance has been obtained from the Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia.

RESULTS

Data were obtained through medical record data collection for the period January-December 2018. During that period, 1 655 pregnant women visited three community health centers with details of 443 at Putat Jaya Community Health Center, 632 at Dupak Community Health Center, and 580 at Perak Timur Community Health Center.

The research results are presented based on the scope of the triple elimination program activities. The first scope of activity is Antenatal Service, Quality Complete Early Detection with variable test coverage, test completeness, and test results. In this study, from Table 1, it is known that the test coverage results obtained at the three community health centers from January to December 2018 reached 100 %. It can be concluded that in the test coverage variable, the three community health centers met the WHO criteria because ≥95 % of pregnant women who visited had been tested in the triple elimination program at the three community health centers.

Table 1

The Coverage of Triple Elimination Program Tests at Putat Jaya Community Health Center, Dupak Community Health Center, and Perak Timur Surabaya Community Health Center in the Period of January-December 2018

	Test Coverage				
Community health center	Number of visits	Tested	Without tested	Percentage	Meet WHO Criteria / No
Putat Jaya	443	443	0	100	Yes
Dupak	632	632	0	100	Yes
Perak Timur	580	580	0	100	Yes

The test completeness variable is divided into 3, i.e., only 1 test, 2 tests, and 3 tests. Based on medical record data for pregnant women who visited three community health centers in the period January-December 2018, the three community health centers met the criteria set out in the triple elimination guidebook by the Ministry of Health of the Republic of Indonesia based on the criteria set by WHO. In 2018, WHO determined that 60 % of pregnant women were thoroughly screened, i.e., HIV, syphilis, and hepatitis. The results obtained in Table 2 show that the three community health centers fulfill the criteria.

Table 2

Completeness of Triple Elimination Program Tests at Putat Jaya Community Health Center, Dupak Community Health Center, and Perak Timur Surabaya Community Health Center in the Period of January-December 2018

Community health center	Number of visits	Test Coverage			Test Category			%	Meet the criteria / not
		HIV	Syphilis	Hepatitis B	Only 1 test	2 test	Complete		
Putat Jaya	443	443	443	443	0	0	443	100	Yes
Dupak	632	590	576	529	44	76	509	80.54	Yes
Perak Timur	580	580	580	580	0	0	580	100	Yes

Table 3 shows the number of patients with each disease at each community health center from January to December 2018. Of the 1 655 pregnant women tested for the triple elimination program, there were 3 HIV cases, 4 cases of syphilis, and 41 cases of hepatitis B according to the total number of the three community health centers. There were no pregnant women who suffered from more than one disease from the three.

Table 3

Number of HIV, Syphilis, and Hepatitis B Patients Recorded in the Triple Elimination Program at Putat Jaya Community Health Center, Dupak Community Health Center, and Perak Timur Surabaya Community Health Center in the Period of January-December 2018.

Community health center	Test Results						
	HIV	Syphilis	HBsAg	HIV+ HBsAg	HIV+ Sifilis	HBsAg+ Sifilis	HIV+HBsAg+ Syphilis
Putat Jaya	0	0	4	0	0	0	0
Dupak	3	4	13	0	0	0	0
Perak Timur	0	0	24	0	0	0	0

The percentage of each disease is presented in Table 4. It is known that HIV had a percentage of 0 % for Putat Jaya Community Health Center, 0.5 % for Dupak Community Health Center, and 0 % for Perak Timur Community Health Center. Of the three health centers, 2 out of 3 community health centers had met WHO criteria regarding a maximum HIV percentage of 0.30 %, i.e., Putat Jaya and Perak Timur Community Health Centers, while Dupak Community Health Center still had a relatively high rate of 0.5 % (3 out of 632) cases found.

Table 4

The Test Results for the Triple Elimination Program at Putat Jaya Community Health Center, Dupak Community Health Center, and Perak Timur Surabaya Community Health Center in the Period of January-December 2018 toward WHO Criteria Based on Surveillance Indicators

Disease	Community health center						Meet the criteria/not
	Putat Jaya		Dupak		Perak Timur		
	Frequency n=443	%	Frequency n=632	%	Frequency n=580	%	
HIV	0	0	3	0.5	0	0	Yes
Syphilis	0	0	4	0.6	0	0	Yes
Hepatitis B	4	0.9	13	2.1	24	4.1	Yes

Syphilis has the maximum criteria for infected pregnant women at 1.70 %. The percentage rate for syphilis in the three health centers studied did not show a high number, i.e., 0 % for Putat Jaya Community Health Center, 0.6 % for Dupak Community Health Center, and 0 % for Perak Timur Community Health Center. Thus, it can be concluded that the three health centers have met the WHO criteria in the number of pregnant mothers with maximum infection against syphilis.

For hepatitis B, the maximum number set by WHO is the highest at 7.10 % because hepatitis B cases in Indonesia are still straightforward to find. It can be seen that hepatitis B cases are the highest percentage, which can be found in Table 4. Three out of 3 community health centers have met WHO criteria with a percentage of 0.9 for Putat Jaya Community Health Center, 2.1 % for Dupak Community Health Center, and 4.1 % for Perak Timur Community Health Center.

The second scope of activity is the handling of positive pregnant women with therapy variables. WHO hopes that according to the indicators set out in the guidelines for the triple elimination program, 100 % of positive pregnant women get treatment. The results of the variables are presented in Table 5. From the figures obtained, Putat Jaya Community Health Center has met the WHO's criteria. Perak Timur Community Health Center did not reach it, while Dupak Community Health Center required further data.

Table 5

Coverage of positive pregnant mother therapy in the triple elimination Program at Putat Jaya Community Health Center, Dupak Community Health Center, and Perak Timur Surabaya Community Health Center in the Period of January-December 2018

Community health center	HIV Therapy			Syphilis Therapy			Hepatitis B			Meet the criteria / not
	Number of positive pregnant women treated	The number of positive pregnant women	%	Number of positive pregnant women	The number of positive pregnant women treated	%	Number of positive pregnant women	The number of positive pregnant women treated	%	
Putat Jaya	0	-	-	0	-	-	4	4	100	Yes
Dupak	3	No data	No data	4	No data	No data	13	No data	No data	No
Perak Timur	0	-	-	0	-	-	24	23	96	No

The third activity scope is delivery with the variable of the place of delivery. These criteria are 100 % positive mothers give birth in health care facilities and are assisted by health personnel. From Table 6, it is known that the data has been obtained. At the Putat Jaya Community Health Center, all pregnant women give birth in health facilities, precisely at the hospital, without specific information. The conclusion that can be drawn is that the Putat Jaya Community Health Center met the WHO criteria in the scope of activities for the delivery of hepatitis B. The Dupak Community Health Center with 3 HIV-positive pregnant women, 4 positive syphilis pregnant women, and 13 hepatitis B positive pregnant women, the scope of maternity activities cannot be presented because no data can be accessed at the community health centers because they were referred to a referral hospital.

Delivery place

Furthermore, Perak Timur Community Health Center had a 100 % percentage in meeting the WHO criteria regarding the place of delivery. It can be concluded that the Perak Puskesmas have met the WHO criteria regarding the place of delivery for positive pregnant women. The fourth and fifth activities' scope is the handling of children from infected mothers, and the results of children's examinations cannot be presented because data were not obtained because they were referred to higher health facilities, i.e., hospitals.

Table 6

The Delivery Place of Positive Pregnant Women in the Triple Elimination Program at Putat Jaya Community Health Center, Dupak Community Health Center, and Perak Timur Surabaya Community Health Center in the Period of January-December 2018

Community health center	Delivery place									Meet the criteria / not
	HIV			Syphilis			Hepatitis B			
	n	Health facilities	%	n	Health facilities	%	n	Health facilities	%	
Putat Jaya	0	-	-	0	-	-	4	4	100	Yes
Dupak	3	No data	No data	4	No data	No data	13	No data	No data	No data
Perak Timur	0	-	-	0	-	-	24	24	100	Yes

DISCUSSION

From the results of the research conducted, it was found that pregnant women suffered from more than one disease from the three infectious diseases simultaneously. This is in line with other studies which found that the prevalence of co-infection among the three diseases was very low (9,10). In Uganda, for example, there was no HBV and HCV co-infection in HIV-positive women (11,12). Co-infection may be influenced by factors such as the prevalence of each infection in specific communities, the risk behaviors involved in the transmission, and the time/age at which maximum exposure to each infection occurred (13). The absence of HBV co-infection in HIV-positive women was due to the absence of risk factors in the study population.

This study showed that the test coverage of the three health centers met the WHO criteria. Factors that could help countries move towards EMTCT HIV and syphilis are the high coverage of ANC services, routine screening for HIV and syphilis in pregnancy, prompt follow-up of seropositive pregnant women and exposed infants, and a well-organized monitoring and surveillance system that captures both national and subnational data (14). A study (15) showed that despite a 1 % (high rate) prevalence of syphilis, elimination of congenital syphilis could be achieved with coverage. ANC >95 %, screening for syphilis >95 %, rapid treatment with benzathine IM in early-pregnancy positive women, and follow-up of exposed infants. In the Americas, for example, research shows that when coverage increases, the number of cases dramatically decreases due to the implementation of well-integrated testing and immunization. In contrast to America, a country with low test coverage, Africa, has resulted in a high prevalence of HIV, syphilis, and hepatitis B (16). This shows that test coverage has a significant impact on the number of cases of the disease.

In 2018, WHO expected 60 % of pregnant women to be thoroughly tested for HIV, syphilis, and hepatitis B. The results showed that the three community health centers were good. There was one community health center, i.e., Dupak Community Health Center, which did not reach 100 % completeness but following the criteria set in 2018. The incompleteness was caused by incomplete medical record recapitulation, which as a source of research data, or because the test was not complete. Completeness of the tests carried out is needed to help the program achieve its targets. Cuba is the first country validated by WHO to be a free MTCT country regarding HIV, syphilis, and hepatitis B. Cuba has coverage data available at the polyclinic level. It is confirmed

in all regions that more than 95 % of pregnant women are thoroughly tested at least once during pregnancy (14).

According to the test results obtained, the prevalence of the three diseases in the three community health centers was low and has met the WHO criteria. The case rate is not presented because the number of cases of infected infants was unknown, and only the number of births was known. For HIV, the WHO criteria set the maximum number of infected pregnant women as 0.30 %, and the management expects 100 % of pregnant women with HIV to be treated with ARVs. From the results of the research, the three community health centers had a very low number of HIV cases, even 0 in both community health centers. The number of cases was found to be low due to 3 possible factors. First, the case rate was low due to the success of the program. The second is the "iceberg phenomenon" in which the number of people detected and identified with HIV is only a fraction of the actual cases because most of them may not have been discovered (17). The third possible cause is due to incomplete data recapitulation in medical records. Complete data summaries are also important aspects that need to be considered. More and more complete input will lead to more and more identified HIV cases so that it can overcome the problem of the iceberg phenomenon and reduce the number of HIV cases in pregnant women, infants, and globally (18). In addition, adequate training of medical personnel is also a crucial issue that should be considered (19). This has also been proven by China, and the programs implemented bring significant changes in China (19).

The WHO criteria for syphilis in triple elimination is a maximum infection prevalence of 1.70 %. In this study, it was found that the prevalence rate of syphilis was very low in the three community health centers. The three community health centers have met the established WHO criteria. Even with very low numbers, the state should not be negligent with the results. Research suggests that the doubling of the congenital rate of syphilis in 2016 in Japan is a result of the reduced public health focus on syphilis due to the perception that syphilis is no longer a significant source of morbidity and mortality (7,20). The low case rate of syphilis represents a strong global response, including the WHO addressing the epidemiology of HIV and congenital syphilis. However, previous research has argued that the WHO guideline, including triple elimination, is sufficient to clear congenital syphilis in a country (7). It argues that a more effective integration strategy is needed. The approach offered is described by a simple analogy. First, "turn off the tap" by controlling cases in the high-risk group or the key population, which are sources including MSM, FSW, Waria, and IDU. The second is "plug up the hole" a preventive movement or preventing transmission from the key population to pregnant women. And the last strategic step that needs to be done is to "dry our the floor" by conducting EMTCT. This is also supported by research that conducted a modeling study in 9 countries in Africa and found that even though the WHO target had been set and global EMTCT was met, none of these countries achieved the goal (21). In conclusion, the elimination of syphilis MTCT globally may be achieved. Still, it is difficult to maintain if syphilis cases in the key population are not well controlled while promoting the integration of syphilis screening in pregnant women.

Furthermore, for hepatitis B, WHO sets criteria in the form of a maximum prevalence of cases in 2018 of 7.10 %. The three community health centers have met the established standards. This does not mean that the number of hepatitis B cases is very low, but it still requires further efforts to get EMTCT. Several studies (22–24) suggest that the numbers recorded are not representative and are estimated to be only 10 % of the actual number of sufferers. Meanwhile, in infants, surveillance for acute hepatitis B infection cannot fully capture the population prevalence of HBV infection because most infections in infants and children are asymptomatic (25). ven as of December 2017, Indonesia was not yet among the 25 countries with HBsAg seroprevalence in children aged 5 years which decreased to <1 % (7).

According to the recommendations set by WHO, babies born should receive Hbvacc-BD immediately for 24 hours. The study found that children who received the vaccine more than 12 hours after birth had a 2.9 times greater risk than children who received the vaccine right after birth or <12 hours. Hepatitis B immunization coverage <24 hours according to health office data in 2018 reached 98.94 %, 100 %, and 89.87

% for community health centers in Putat Jaya, Dupak, and Perak Timur, Surabaya, respectively. The program that has been implemented was estimated to be able to prevent 37 million cases of chronic HBV infection and more than 7 million hepatitis B-related deaths during the lifetime of children born between 1990 and 2014 who did not have a hepatitis B vaccination program (26). In Indonesia, the results of PMTCT programs regarding HBV have not been systematically evaluated to date. Identifying the progress of the HBV MTCT will facilitate further projection and target setting. Also, understanding the factors related to program outcomes is very important to understand better how policies and programs will be established (25).

According to WHO recommendations, HIV-positive pregnant women should be treated with ARV in the form of a Fixed-Dose Combination, which is consumed once a day, for life with coverage of 100 %. For syphilis-positive pregnant women, 100 % of pregnant women were treated with Benzathine Penicillin G 3.4 million IU IM single dose in the early phase, repeated 2 times with an interval of 1 week or referred. Furthermore, for hepatitis B-positive pregnant women, 100 % of patients must be referred. Following these guidelines, 1 community health center has met these criteria, i.e., Putat Jaya Community Health Center, while the other 2, the data were not available because they were referred to a referral hospital and did not meet. In Putat Jaya Community Health Center, 100 % of pregnant women who were positive for hepatitis B received treatment by referral while at Perak Timur Community Health Center only 96 %.

According to the data obtained, 2 out of 3 community health centers have met the specified criteria, i.e., 100 % of pregnant women give birth in health facilities. The figures obtained must be maintained and are expected to exist in all community health centers and hospitals in Indonesia. Additional policies can also be an applied solution. China has a national policy that requires pregnant women to give birth in health facilities to reduce maternal and infant mortality rates (27). Another aspect to consider is that the hospital level is related to the risk of MTCT. It was also found that MTCT rates were higher for children sent to district-level hospitals or below than for those assigned to regional or referral hospitals with complete facilities (25). Other considerations referred to are the management of vaccination procedures and knowledge of medical personnel. However, the authors also said that further research is needed. Furthermore, the last one for the variable handling of children from infected mothers and the results of examinations in children did not get data because they were referred to the hospital.

CONCLUSION

The triple elimination program at three community health centers has met the WHO criteria. The number of cases of the three diseases is low in pregnant women (below the maximum percentage of infected pregnant women) with no pregnant women who suffer from more than one disease from three infectious diseases. WHO criteria regarding the triple elimination program at Putat Jaya, Dupak, and Perak Timur Community Health Centers in Surabaya are fulfilled in the quality of complete antenatal care and early detection activities, but the data was incomplete for Dupak Community Health Center in the handling of pregnant women with positive results, and childbirth. Examination results activities on children and the handling of children from infected mothers require further data.

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Disclosure

There were no conflicts of interest in this research conducted.

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COVID-19 and hepatitis B Ambassador of Surabaya, Indonesia: Motivation, commitment, and knowledge of youth generation towards health programs in the pandemic era

COVID-19 y Hepatitis B Embajador de Surabaya, Indonesia: Motivación, compromiso y conocimiento de jóvenes generaciones hacia programas de salud en la era pandémica

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SUMMARY

Background: *To curb Corona Virus Diseases 2019 (COVID-19) pandemic and Hepatitis B further spread, the local Health Ministry collaborated with local communities to build COVID-19 and Hepatitis B Ambassador. This program utilizes the youth generation to support health promotion and health prevention. This study aims to evaluate the motivation, commitment, and knowledge of the youth generation as very few studies have attempted to analyze them.*
Methods: *Fifty-seven participants who participated in the Ambassador program were voluntarily enrolled in the study. We conducted an online survey and presented them with a questionnaire while monitoring*

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their progress in the live video call. The qualitative and quantitative data were analyzed statistically to find the correlation between the variables.
Results: *The youths' motivation for joining health programs comprises benefit-driven motivation and mostly altruistic motivation. Most of the youth participants gave a high number of commitment percentages and good opinions regarding both disease management by the local government. There is a significant correlation between the participants' commitment with their knowledge regarding Surabaya and COVID-19 (p<0.001), but not with hepatitis B (p=0.153). There is a significant positive correlation between participants' knowledge of Surabaya city with knowledge of COVID-19 (r=0.255; p=0.018) and Hepatitis B (r=0.331; p=0.003). The participants' age affects their commitment significantly (p<0.001).*
Conclusion: *The motivation, commitment, and knowledge of the youth generation that joining the health ambassador program were correlated with each other. These findings might give an insight, especially for the government to encourage the youth generation to help supporting health promotion and health prevention.*

Keywords: *Motivation, commitment, knowledge, COVID-19, hepatitis B, Ambassador, youth.*

RESUMEN

Antecedentes: *Para frenar la pandemia de enfermedades por el virus de la corona 2019 (COVID-19) y la propagación de la hepatitis B, el Ministerio de Salud local colaboró con las comunidades locales para construir COVID-19 y hepatitis B Embajador. Este programa utiliza jóvenes generaciones para apoyar la promoción de la salud y la prevención de la salud. Este estudio tiene como objetivo evaluar la motivación, el compromiso y el conocimiento de la generación joven, ya que muy pocos estudios han intentado analizarlos.*
Métodos: *Cincuenta y siete participantes del programa Ambassador se inscribieron voluntariamente en el estudio. Se realizó una encuesta en línea y se presentó un cuestionario mientras se monitoreaba su progreso en la videollamada en vivo. Los datos cualitativos y cuantitativos se analizaron estadísticamente para encontrar la correlación entre las variables.*
Resultados: *La motivación de los jóvenes para unirse a los programas de salud comprende la motivación impulsada por los beneficios y la motivación mayoritariamente altruista. La mayoría de los jóvenes participantes dieron un alto número de porcentajes de compromiso y buenas opiniones con respecto al manejo de la enfermedad por parte del gobierno local. Existe una correlación significativa entre el compromiso de los participantes con su conocimiento sobre Surabaya y COVID-19 (p<0,001), pero no con la hepatitis B (p= 0,153). Existe una correlación positiva significativa entre el conocimiento de los participantes de la ciudad de Surabaya con el conocimiento de COVID-19 (r= 0.255; p= 0.018) y Hepatitis B (r= 0.331; p= 0.003). La edad de los participantes afecta significativamente su compromiso (p<0,001).*
Conclusión: *La motivación, el compromiso y el conocimiento de jóvenes generaciones que se unieron al programa de embajadores de la salud se correlacionaron entre sí. Estos hallazgos podrían dar una idea, especialmente para que el gobierno aliente a la generación de jóvenes a ayudar a apoyar la promoción y la prevención de la salud.*

Palabras clave: *Motivación, compromiso, conocimiento, COVID-19, hepatitis B, Embajador, juventud.*

INTRODUCTION

Since March 2020, Indonesia has been dealing with the new Corona Virus Diseases 2019 (COVID-19) pandemic, and the incidence has been increasing up dramatically until October 2020. Data from the Health Ministry of Indonesia showed that COVID-19 cases have spread almost into all provinces nationwide and the highest prevalence was documented in Java islands (1). Java is the most populous island in the world with an estimated 152.4 million population living in 2020 (2). Among big cities in the Java islands facing difficult conditions during the pandemic era, Surabaya is the second biggest city in Indonesia comprising a population of more than 2.9 million (3). The huge population often corresponds to the high risk of infectious disease transmission (4). Indeed, data from the Health Ministry of Indonesia shows that Surabaya has a high level of COVID-19 spread in pandemic (1).

Several programs were made by the health ministry of Surabaya to control COVID-19 transmission including health promotion and health prevention (5). These programs need a good method for disseminating information to all population sectors throughout Surabaya city and internet-based technology (e.g. by social media and online article) can be a good choice (6). Several studies from different countries have proven that this method has a robust impact (6-9). Furthermore, the utilization of internet-based

technology can also reduce the direct face-to-face interaction between health educators and population targets during the pandemic.

Besides COVID-19, hepatitis B also became a special concern for the local health ministry. This is because Surabaya had the highest incidence of hepatitis B in East Java Province (219 of 432 total cases) according to the Health Ministry of East Java Province(10). Several factors might be related to the high prevalence of these diseases including educational and socioeconomic levels. Good health promotion and health prevention programs are crucial to stop the hepatitis B chain of infection for the lower educational and socioeconomic levels of the Surabaya population.

Surabaya still facing many problems of health programs regarding COVID-19 and hepatitis B. Factors such as wrong community believes, hoaxes (either mis- or dis-information), and other wrong health issues give a huge impact on the success rate of the health program (11). For example, there was wrong community believes said that immunization or vaccination of COVID-19 and Hepatitis B was not appropriate for local religion (12). Indeed, this wrong community believes made the immunization scope of Hepatitis B almost did not reach the national target in 2017 and bring up some polemics issues regarding upcoming COVID-19 vaccines in 2020 (13-15). People especially from low educational and socioeconomic levels, which health promotion somehow difficult to reach, easily believe any kind of health issue. They got these issues from mass media either non-electronic (e.g. illegal leaflet) or electronic (e.g. social media). Special for social media, this electronic media is a well-known main source of hoax spread all over the world including Indonesia, one of the biggest Internet user countries in the world (16,17). The local health ministry needs to withstand those issues with optimization of health promotion, but it seems difficult since many other health problems also need to be prioritized. Therefore, the help and support of the appropriate member community, especially those who close to digital technology, are essentially desired to reach many levels of Surabaya citizens as the main target of the health program. One candidate of this appropriate member community is the youth generation.

The role of the youth generation as the closest generation to digital technology is needed to increase the scope target of health promotion and health prevention (18). The fact that the general population of Surabaya was dominated by young adults supported the idea to build an innovation program exploiting the critical role of the youth generation. This innovation program, called COVID-19 and hepatitis B Ambassador Surabaya, was built by the Health Ministry of Surabaya, Universitas Airlangga, and several youth communities to tackle COVID-19 and hepatitis B problems by improving health promotion and health prevention. Several studies explained the role of health ambassadors countering health problems in the communities (19-21), but studies that explore the motivation and commitment of the youth generation to become a health ambassador have not been extensively studied yet. This study aimed to depict the interest of the youth generation to curb COVID-19 and hepatitis B by joining a health ambassador program. We described their motivation to join the ambassador program, their commitment, and their knowledge regarding Surabaya, COVID-19, and hepatitis B. Besides, we analyzed the correlation between the respondents' age and their commitment as well as their commitments and the degree of their knowledge. This study is important to give insight, especially for the government to encourage the youth generation to participate in and supporting health promotion and health prevention.

METHODS

Design, participants, and setting

The COVID-19 and hepatitis B Ambassador is a youth community built by the Health Ministry of Surabaya, Universitas Airlangga, and several youth communities. The member of the ambassador was selected based on several steps and criteria. This study sought to explore the underlying motivation of the youth generation in joining the ambassador selection program and their knowledge about COVID-19, hepatitis B infection, as well as Surabaya city. This study employed an analytical cross-sectional design. The participants under investigation

were the youth generation who signed up in the COVID-19 and hepatitis B Ambassador Selection program. To recruit the participants, we were put up promotional flyers at several university campuses and schools also social media platforms (Instagram and Facebook) targeted at those who were interested in becoming members of the ambassador. The youth generation was chosen as the main subject of this study because the study primarily aims to investigate the youth's roles as intermediaries between society and social services. The youths have unique perspectives of social roles designed for the promotion of community health.

The inclusion criteria were people aged between 15 and 30 years old and who were currently staying in Surabaya. These ages were selected according to the definition of youth by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) as well as other countries in Southeast Asia including Indonesia policy (22-24). From a total of ±100 participants who registered for the program, 86 participants were recruited according to the inclusion criteria of the study. The exclusion criteria are those who were not willing to participate in the survey. A total of 57 participants managed to complete all of the questions provided and were subsequently analyzed.

Data Collection Procedures

As a sample for the investigation, a group was chosen which comprised young people who actively participated in the COVID-19 and hepatitis B Ambassador program. All participants of this group voluntarily took part in this study. At the beginning of the program, we sincerely and politely invited each participant to participate in the program evaluation. We informed the participants that participation was completely voluntary and that they had the right to withdraw from the survey at any time.

In the beginning, we collected demographic data of the participants using a questionnaire. The investigators established another self-validated questionnaire consisting of quantitative components and qualitative components. They included a set of multiple-choice questions, which assess participants' knowledge of Surabaya city, COVID-19 disease, and hepatitis B disease, and several open-ended questions, which assess participant's commitment level and motivation in attending this ambassador program. To ensure integrity during this process, the participants answered the questionnaire online through the Google forms portal while the investigators monitored the participants through the zoom platform.

Data analysis

The results of the questionnaire were coded in SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, Ill., USA), and statistical analysis is conducted. We analyzed the quantitative data, using descriptive statistics. We compared several variables through paired t-tests. Further, each estimated effect was provided with a 95 % confidence interval and a 5 % level of significance. The qualitative data were analyzed by conducting a content analysis of all of the responses. Similar responses were grouped into several categories.

RESULTS

1. Sociodemographic characteristics of the participants

The Sociodemographic characteristics of the participants varied as shown in Table 1.

From 57 participants collected, the genders of the participants were dominated by females (68.4 %). Meanwhile, the age of participants is dominated by those under 20 years old (61.4 %). In terms of education, the participants were in or had done High School (7.0 %), Diploma (12.3 %), and bachelor's degree (80.7 %). Education and occupation are dominated by people related to the medical and health job. The majority of the participants' place of current residence was East Surabaya (57.9 %).

2. Participants Motivation and Commitment

Concerning motivation to join the ambassador program, our data showed that there were two

Table 1

Sociodemographic characteristics of the participants (n = 57)

Variables	Freq (n)	%
Gender		
Male	18	31.6
Female	39	68.4
Age (years)		
15-20	35	61.4
21-30	22	38.6
Education		
Senior High School	4	7.0
Diploma	7	12.3
Medicine and Health	5	8.8
Others	2	3.5
Bachelor	46	80.7
Medicine and Health	20	35.1
Others	26	45.6
Occupation Status		
High School Students	2	3.5
College Students	46	80.7
Office Workers	7	12.3
Medicine and Health	1	1.8
Others	6	10.5
Unemployment	2	3.5
Place of current residence		
Central Surabaya	7	12.3
East Surabaya	33	57.9
West Surabaya	3	5.3
North Surabaya	4	7.0
South Surabaya	10	17.5

major categories of motivation named benefit-driven motivation and altruistic motivation (Table 2).

A large majority of our participants (87.0 %) have altruistic motivation. Altruistic motivation consists of the desire to enhance the welfare of others instead of oneself. This includes the hope to be able to curb the COVID-19 and Hepatitis B infection cases through health promotion, give social support to maintain health, and contribute to society. The majority of the participants (68.4 %) felt a strong need to suppress the infection rate of COVID-19 and hepatitis B infection by participating in the ambassador program.

Some participants also have benefit-driven motivation such as the expansion of social networks, gaining new knowledge, gaining new experience, and developing public speaking skills. About 45.0 % of our participants admitted to having these benefit-driven motivations. This shows an exchange between the ambassador's contribution to the campaign activity and the ambassador's benefits in return. Gaining new experience and new knowledge both present as the highly ranked benefits expected by the participants.

Table 2

Motivations of the participants

Motivation	Freq (n)	%
Altruistic motivation		
Help to suppress COVID-19 and Hepatitis B burden through health promotion	39	68.4
Provide social support to maintain health	9	15.8
Contribute to society	6	10.5
Self-centered motivation		
Gain new experience	14	24.6
Gain new knowledge	14	24.6
Develop communication skills	7	12.3
Social networking	6	10.5

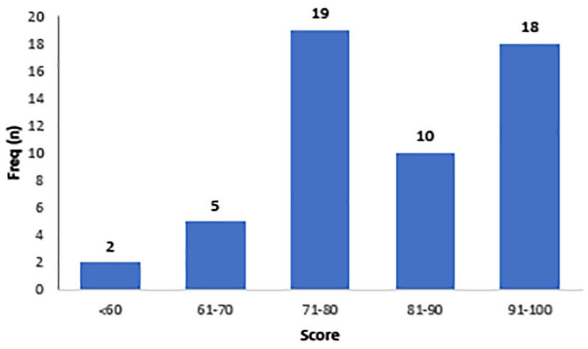

Figure 1. Participant commitment to join and active in the ambassadors' program.

Each frequency of commitment level was shown in Figure 1. Of all participants, 35.2 %, falls between 71.0 to 80.0 %. While 33.3 % of participants committed 91.0 – 100 % of their effort to this ambassador program. Further analysis regarding different commitment between men and women participants showed an

insignificant result (p= 0.328) (Supplementary Table 1).

3. Their opinion regarding COVID-19 and Hepatitis B condition in Surabaya

We measure qualitatively COVID-19 and hepatitis B from the participants. The open question was "What do you think about the current condition of Surabaya in the face of high cases of Hepatitis B and COVID-19? Give your good advice to the city government; the people of Surabaya and this ambassador in the future."

From all participants, 48.0 % of participants' shows good enough result, with 31.0 % worry about the condition, 19.0 % very worrying condition and only 2.0 % shows the government achieves very good performance (Figure 2).

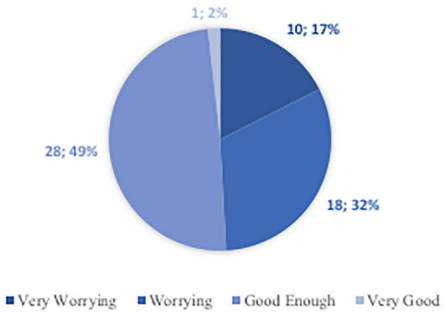

Figure 2. Opinion regarding COVID-19 and Hepatitis B condition in Surabaya (n=57).

4. Participants Knowledge Regarding Surabaya, COVID-19, and hepatitis B

We measure quantitatively the knowledge of participants (n=57) about the knowledge of Surabaya, hepatitis B, and COVID-19 with multiple-choice questions. The variety of results is figured in Figure 3. There was no cut-off definition that has a high score or low score in this questionnaire.

In COVID-19 knowledge, most participants gain a score of 60. In hepatitis B knowledge, most participants achieve a score of 80. And from the knowledge of Surabaya City, most participants achieve a score of 70. In addition, we also compare the participants' knowledge of men and women (Table 3).

In general, knowledge regarding Surabaya, COVID-19, and hepatitis B were higher for male participants compared to female participants. This was shown as the mean of men's knowledge of Surabaya (72.22), COVID-19 (68.89), and hepatitis B (90.00) were higher than women's, but further statistical analysis showed that only knowledge of hepatitis B was significantly different between men and women (p= 0.003) (Table 3).

Furthermore, we also analyzed the correlation between the participants' knowledge regarding Surabaya to the knowledge of COVID-19 and hepatitis B (Table 4).

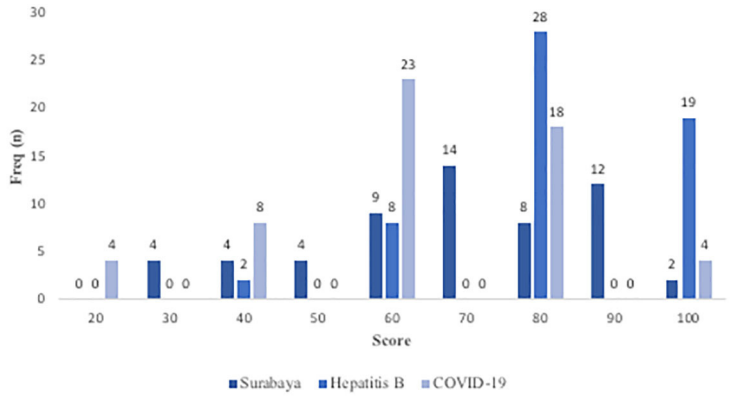

Figure 3. The participant score for three consecutive questions about the knowledge in Surabaya, Hepatitis B, and COVID-19.

Table 3

Knowledge of Surabaya City, COVID-19, and hepatitis B between male and female participants

Variables	Mean	Median	Minimum	Maximum	SD	t-test		
						t	df	P
Knowledge of Surabaya								
Men	72.2	70.0	40	90	15.2	1.045	43.4	0.302
Women	67.2	70.0	30	100	20.3			
Knowledge of COVID-19								
Men	68.9	80.0	20	100	23.0	1.276	27.4	0.213
Women	61.0	60.0	20	100	18.3			
Knowledge of Hepatitis B								
Men	90.0	90.0	80	100	10.30	3.073	49.9	0.003**
Women	79.0	80.0	40	100	16.5			

**Significant <0.01

Table 4

Correlation of the participants' knowledge regarding Surabaya to the knowledge of COVID-19 and hepatitis B

Variables	n	r	p
Participants' knowledge regarding COVID-19	57	0.255	0.018*
Participants' knowledge regarding Hepatitis B	57	0.331	0.003**

*Significant <0.05; **Significant <0.01

There was a positively weak yet significant correlation between participants' knowledge regarding Surabaya to the knowledge of COVID-19 (r= 0.255; p= 0.018) and hepatitis B (R= 0.331; p= 0.003).

5. Correlation between commitments to the degree of knowledge and age

This study showed a significant correlation between the participants' commitment with their knowledge regarding Surabaya and COVID-19 but not with hepatitis B. These results were proven by p<0.001 after statistical analysis measuring those variables (Table 5). On the other hand, the participants' age affects the devoted commitment proposed by the participants significantly (p<0.001). It seems young adult participants are compliant to provide more effort to become the ambassador.

Table 5

Correlation between commitments to the degree of the knowledge

Variables	t	df	p
Participants knowledge regarding Surabaya	-5.519	56	0.000*
Participants knowledge regarding COVID-19	-7.485	56	0.000*
Participants knowledge regarding hepatitis B	-1.450	56	0.153

**Significant <0.01

DISCUSSION

This study depicts the interest of the youth generation to withstand COVID-19 and hepatitis B by joining a health ambassador program. The sociodemographic of youth generation as participants in this study was varies and encompass all region of Surabaya. The majority motivation to join the ambassador program was they want to help to suppress COVID-19 and hepatitis B burden through health promotion along with gaining new experience. The commitment was majority high. Their knowledge regarding Surabaya, COVID-19, and hepatitis B were generally good, especially for understanding the diseases. The statistical analysis showed that the participants' age was correlated with their commitment. Only participants' knowledge regarding Hhpatitis B was different between men and women. There was also a positive correlation of participants' knowledge regarding Surabaya to the knowledge of COVID-19 and hepatitis B. Furthermore, the analysis also revealed that commitments were correlated with the knowledge regarding Surabaya and COVID-19 but not with hepatitis B.

From the demographic data of participants that were collected, the participants were dominated by females. This is in accordance with the population of Surabaya in 2019, where the government data showed that the number of females (50.59 %) is more than male (49.41 %) (25). These findings supported a theory that health promotion related to social activities is usually dominated by females (26). Furthermore, college women had better interpersonal relationships and health responsibilities compare to college men (27,28).

The demographic data also revealed that in terms of education, the majority of the participants who were interested to join the ambassador program were in or had done a Bachelor's degree. This is concordant with a study carried out by Yang et al, which showed that educational level had a positive correlation with health literacy (29). Higher education levels seem to have higher interest to join positive social activities including health programs. This might because education is a fundamental social determinant of health, which is an upstream cause of health (30).

In this study, education and occupations are dominated by participants with health-related backgrounds. This result was in line with a previous study that showed that people who majored in medical fields had positive health-promoting lifestyles. An individual with medical knowledge background can encourage a community to adopt health-enhancing behaviors (31). Special for college students, those who took medical majors had better cognitive understanding and perception of health information than those who took nonmedical majors. A previous study also showed that college students with medical majors were more willing to engage in appropriate health behaviors. This willingness is explained by the fact that medical majors' campus trains them to conduct health promotion for the community (32,33).

The altruistic motivation displayed in the data represents public service motivation (PSM). PSM is defined as the beliefs, values, and attitudes beyond organizational and self-interest, which also corresponds to the interest of the larger political body, and inspires individuals to act accordingly (34). PSM put motives and actions directed to serve the community as a central theme. There are three kinds of motives revolving around public service. Rational motives refer to people's desire to contribute to good public decision-making as a social responsibility or as a self-esteem enhancement. Norm-based motives refer to aspirations to maintain social equity by serving the nation or public interest. Affective motives involve emotional bonding with service users and compassion, which can lead to self-sacrifice. Helping to suppress COVID-19 and Hepatitis-B infection is included as rational motives. The willingness to contribute to society is regarded as norm-based motives. Lastly, the desire to provide social support for the community refers to affective motives (34).

Gaining new experience and new knowledge become the two highly ranked benefits expected by the participants from joining this ambassador program. As expected, other ambassador programs provide the opportunity for the participants to gain professional or "soft skills" to ensure success in future endeavors. While this ambassador program generally caters to society at large as its primary goal, it serves as an equally valuable but unstated goal of developing

ambassadors' skills and attitudes. This program also provides an avenue for networking with other professionals, more senior ambassadors, and perhaps other senior stakeholders (35).

It is worth mentioning that the lowest participation rate in volunteering for community services was among people below 35 years old and above 65 years old (36). This tendency showed that youth participation in community service was low and factors such as lack of motivation might be the reason. Therefore, public stakeholders should consider the motivation that drives the participation of youths in ambassador programs while promoting youth volunteering for community services (37).

This study asserted the ambassadors' opinion on COVID-19 and hepatitis B in Surabaya. The devastating effect of the COVID-19 pandemic and the speed of government tackling the issue might affect the opinion of the participants regarding their satisfaction with the governmental pandemic management. In other countries, the satisfaction of the participants towards COVID-19 was affected by how the government controls the virus spread by optimization of their management (38). Specific in Surabaya, the pandemic curve was not showing any massive increase and tends to stagnate. One reason was that the local health ministry did a proactive action to apply for several programs either online or offline classic lectures and workshops for health workers to increase the quality of COVID-19 management. These programs were proved to be effective to increase the knowledge and skill of health workers, therefore their management more optimum (39). This might be a reason for the majority of participants' opinion that said the management of COVID-19 in this city was "good enough". In concordance with COVID-19, data from the Health Profile of Surabaya in 2018 report shown that Surabaya had 0 cases of Hepatitis B even though there were 1 154 positive cases of Hepatitis B in the 2017 report (13,40). This 2018 report might become the reason why Surabaya people did not give special attention to Hepatitis B and thought that hepatitis B control management was "good enough" as well as COVID-19. The participants' answers were often related to the number of cases only as of the parameter of good management.

Generally, our study showed that males had better knowledge than females even though the statistical analysis only showed significant differences in the hepatitis B topic. This was concordant with a study conducted in a developing country, which showed that the mean of men's knowledge was higher than women's regarding health issues (41). In contrast, another study from a different country found that women had better knowledge of HBV transmission modes than men (42). This phenomenon seems to depend on the population and the health topic that was carried out. Furthermore, women seem to easily have a psychological impact more than men. That might affect their knowledge, especially in this pandemic era. This theory supported by a study from China showed that females were significantly associated with the higher psychological impact of the COVID-19 outbreak and preventive measures (43).

Our study showed that there was a positive correlation between the participants' knowledge of Surabaya with COVID-19 as well as hepatitis B. This means that higher knowledge of Surabaya might affect higher knowledge of both diseases. This result might be explained by a theory of Social Capital (SC). The theory explained that there were seven dimensions of SC: Social participation, social network, civic participation, social support, trust, the norm of reciprocity, sense of community (44). SC can contribute to the field of health promotion especially in developing countries (45-47). In this research, knowledge about Surabaya city could be included as a component of social capital that increases the sense of community. Increasing the sense of community contribute to health promotion, therefore, increase the knowledge of the community regarding COVID-19 and Hepatitis B in Surabaya.

This study revealed a significant correlation between the participants' commitments to the knowledge of COVID-19 and Surabaya but not with hepatitis B. Several studies showed that the number of health promotion programs was improved tremendously especially in this pandemic era. The aim of the program mostly to inform some knowledge regarding COVID-19 hence people's awareness shall improve quite significantly (48). In concordance with the previous study, our participants who had good

knowledge regarding COVID-19 and Surabaya were looked more confident and willing to devoted more commitment so they can contribute better (49). Special for Hepatitis B knowledge, the participants' knowledge was generally high either in the low or high commitment participants. This made the correlation became not significant. In addition, the fact that commitments have a significant correlation to the degree of knowledge reflects that commitment is important for increasing the knowledge of youths regarding health topic.

Our study showed that age was correlated with participants' commitment to join the program. Supports our result, another study showed that young adults have more conscience regarding health issues and more capable to manage their health problems (50). Those qualities enable young adults in this study to participate more significantly to prevent health problems. Young adults can determine more important information, qualified ones, so the risk of biased information is smaller (51).

CONCLUSION

COVID-19 and hepatitis B became a special concern for the Surabaya health ministry. The support from the youth generation as the closest generation to digital technology is essential to increase the scope of the target of health promotion and health prevention. This study showed the major motivation for the participants to join the program was benefit-driven motivation. A significant correlation between the participants' commitments to the degree of knowledge reflects that commitment is an important factor to increase the knowledge of youths regarding health topics. Increasing youth knowledge regarding their city could give a positive correlation to their knowledge of diseases. Knowing the motivation, commitment, and knowledge of the youth generation is the important step to gain the support of youths in health promotion programs.

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Supplementary

Supplementary Table 1. Commitment to join the ambassador program between men and women participants

Variables	Mean	Median	Minimum	Maximum	SD	t-test		
						t	df	p
Commitment								
Men	82.9	80.0	65	100	10.7	-0.993	33.8	0.328
Women	86.2	85.0	50	100	12.7			

From the table above, we could see that that women had higher commitment than men even though this difference was not significant. This finding is in concordance with a study by Bayati *et al* in 2018 that found that women ambassadors had better health literacy than men (52). Better health literacy might encourage women ambassadors to build self-confidence in educating and promoting health knowledge. Furthermore, high confident might affect their commitments to join the health ambassadors program.

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Relationship on the performance of doctors in inpatients towards the level of patient satisfaction

Relación del desempeño de los médicos en pacientes ingresados relativo al nivel de satisfacción del paciente

Ilham Daud Samodra[1*], Tjatur Prijambodo[2*•], Musa Ghufron[3*], Sri Widyaningsih[4*]

SUMMARY

Introduction: *The hospital is one place that provides personal health services in the short term and long term. Assessing hospital's quality of service can be seen from the satisfaction of patients who seek treatment. This study aimed to determine inpatient clinic patients' characteristics and the relationship between doctors' performance and satisfaction levels of inpatients.*
Methods: *This study was descriptive-analytic with a cross-sectional approach. The population is the inpatients of Aisyiyah Siti Fatimah Hospital in Sidoarjo, Indonesia. The instrument used was primary data collection using questionnaires. The data obtained in this study were analyzed with the Spearman correlation.*
Results: *Among 100 respondents, there were 45 males and 55 females. The age of most respondents was 25-34 years. The tangible, reliability, responsiveness, assurance, and empathy variables had a range value of 252-327, indicating that the patient was satisfied. There was a significant relationship between the doctor's performance, including tangible variable (p=0.001), reliability variable (p=0.001), responsiveness variable (p=0.001) and assurance variable (p=0.001), and patient satisfaction. However, there was no significant relationship between the empathy variable with patient satisfaction (p=0.256).*
Conclusion: *The performance of doctors in inpatient was associated with the level of patient satisfaction at Aisyiyah Siti Fatimah Hospital, Sidoarjo, Indonesia.*

Keywords: *Patient satisfaction, doctor's performance, hospital.*

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RESUMEN

Introducción: *El hospital es un lugar que brinda servicios de salud personal a corto y largo plazo. La evaluación de la calidad del servicio del hospital se puede ver en la satisfacción de los pacientes que buscan tratamiento. Este estudio tuvo como objetivo determinar las características de los pacientes hospitalizados y la relación entre el desempeño de los médicos y los niveles de satisfacción de los pacientes hospitalizados.*
Métodos: *Este estudio fue descriptivo-analítico con enfoque transversal. La población son los pacientes hospitalizados del Hospital Aisyiyah Siti Fatimah en Sidoarjo, Indonesia. El instrumento utilizado fue la recolección de datos primarios mediante cuestionarios. Los datos obtenidos en este estudio se analizaron con*

la correlación de Spearman.
Resultados: *Entre los 100 encuestados, había 45 hombres y 55 mujeres. La edad de la mayoría de los encuestados era de 25 a 34 años. Las variables tangible, confiabilidad, capacidad de respuesta, seguridad y empatía tuvieron un valor de rango de 252-327, lo que indica que el paciente estaba satisfecho. Hubo una relación significativa entre el desempeño del médico, incluida la variable tangible (p=0,001), la variable de fiabilidad (p=0,001), la variable de respuesta (p=0,001) y la variable de seguridad (p=0,001) y la satisfacción del paciente. Sin embargo, no hubo relación significativa entre la variable empatía con la satisfacción del paciente (p=0,256). Conclusión: El desempeño de los médicos en hospitalización se asoció con el nivel de satisfacción del paciente en el Hospital Aisyiyah Siti Fatimah, Sidoarjo, Indonesia.*

Palabras clave: *Satisfacción del paciente, desempeño del médico, hospital.*

INTRODUCTION

A hospital is a place that provides individual health services in the short and long term. The hospital has several services, including inpatient services, outpatient services, emergency services, and medical services. The quality of service in the hospital is influenced by providing services, facilities, and infrastructure. A hospital must provide safe, quality, and effective services by prioritizing the interests of patients (1,2). The most crucial goal in health service is beneficial outcomes for patients. The level of patient satisfaction determines the measure of the success of service delivery. Service patient satisfaction is achieved when the patient receives the service as required and expected (3).

To determine whether the quality of service from the hospital is good or not, it can be seen through patient satisfaction (4,5). Patient satisfaction is a patient's feeling of the current hospital service performance. Patient satisfaction is the essential aspect of measuring the hospital service, whether it is not the habit or behavior of using hospital services repeatedly (interest in returning). Patient satisfaction can be influenced by several aspects: product characteristics, price, service, location, facilities, profile/image, design, atmosphere, and communication (6,7).

The doctor's performance means the doctor's effort in curing patients with the abilities and skills he has in a certain period with existing conditions. The doctor's performance can be assessed from various sources, including medical records, patient surveys, hospital performance reports, and administrative data. According to the Joint Commission on Accreditation of Healthcare Organization (JCAHO), there are several categories in doctor performance research, namely patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and system-based practice (8). Apart from patient satisfaction, the quality of service at the hospital already has a standard set by the Indonesian Ministry of Health, one of which is the Bed Occupancy Rate (BOR). In the 2012-2016 period, there was an increase in the number of beds to support East Java hospitals' quality of service. In the 2012-2016 period, there was a decrease in the average use of beds. In the 2012 period, the average BOR value was 70.27 %, and in the 2013 period, it experienced a slight decrease of 64.65 %. In the 2014 period, it experienced a rapid decline of 54.6 %, and in the 2016 period, it had increased by 59.4 %, but the BOR had not met the standards set by the Indonesian Ministry of Health between 60 %-85 % (9). Based on this background, this study aimed to determine the relationship between doctor's performance and satisfaction levels of inpatients at Aisyiyah Siti Fatimah Hospital, Sidoarjo, Indonesia.

METHODS

This type of research is observational with a quantitative approach. This research method is a survey with a cross-sectional approach where the data collection process is carried out at the same time between the independent variable and the dependent variable on the research subject, namely patients who have received inpatient services at Aisyiyah Siti Fatimah Hospital, Sidoarjo, Indonesia. The research population was all hospitalized patients at Aisyiyah Siti Fatimah Hospital, Sidoarjo, Indonesia. The instrument of patient satisfaction was assessed based on the aspects of satisfaction assessment is tangible, reliability, responsiveness, assurance, and empathy (10).

In this study, researchers used the Statistical Package for the Social Sciences (SPSS) application Version 25. The stages in data processing include examining all collected data (editing), providing specific numbers or codes that have been agreed upon from the questionnaire (coding). After that, input the data according to the code that has been determined for each variable (Data Entry) (11).

This study used univariate and bivariate data analysis. Univariate research is used to assess the distribution and normality of data from existing variables. This bivariate study was to determine whether there was a relationship between two variables, namely the doctor's performance variable in the form of ordinal data and the patient's satisfaction variable in the form of ordinal data. From the purposive sampling sample that has been obtained, the SPSS version 25 application was used. Validity and reliability tests were performed. After testing the validity and reliability, the Spearman correlation test was carried out to determine whether there was a relationship between the dependent and independent variables. The test used a 95 % degree of confidence so that the p-value was ≤ 0.05, indicating that the statistical calculation was significant or a relationship between the doctor's performance and the level of patient satisfaction in hospitalization. If the p-value was ≥ 0.05, which means it is not significant or indicates that there is no relationship between the doctor's performance and the level of patient satisfaction in hospitalization (11).

RESULTS

Characteristics of respondents

Based on the results of research on 100 respondents in Table 1, it can be seen that 45 people are male and 55 people are female.

Table 1

Characteristics of respondents

Characteristics	Categories	n	Percentage
Sex	Male	45	45
	Female	55	55
Age	18-24 years	16	16
	25 - 34 years	25	25
	35 - 44 years	16	16
	45 - 54 years	16	16
	55 - 64 years	17	17
	> 65 years	8	8
Education Level	Primary school	16	16
	Junior high school	18	18
	Senior high school	54	54
	Bachelor degree	12	12
Occupation	Farmer	6	6
	Entrepreneur	27	27
	Civil servants	2	2
	Police	1	1
	General employees	13	13
	Retired civil servants	6	6
	Does not work	45	45
Cost Insurers	Personal	30	30
	Office	0	0
	Insurance	7	7
	BPJS (Insurance and Social Security)	63	63
Total		100 people	100

Comparison of the number of responses taken between men and women did not differ much. For the age of the respondents, the majority were 25 people (25 %) aged 25-34 years. For the latest education, it is known that the majority of the respondent with high school education is 54 people (54 %). The majority of respondents' professions were 45 people (45 %) who do not have a job. For the cost insurers, the majority of respondents were 60 people (60 %) who use BPJS (Insurance and Social Security).

Patient satisfaction level

The patient satisfaction level category was calculated with the following interval results: very dissatisfied if the value was 100-175, dissatisfied if the value was 176-251, satisfied if the value was 252-327, and very satisfied if the value was 328-403. Based on Table 2, it can be seen that the tangible, reliability, responsiveness, assurance, and empathy variables have a value is 252-327, which means that the patient was satisfied. At the level of satisfaction, all variables had a level of satisfaction at the satisfaction level.

Table 2

Calculation of patient satisfaction level based on tangible, reliability, responsiveness, assurance, and empathy variables

Nº	Variable	Value	Conclusion
1	Tangible	307	Satisfied
2	Reliability	309	Satisfied
3	Responsiveness	312	Satisfied
4	Assurance	312	Satisfied
5	Empathy	314	Satisfied

Relationship between doctor performance in inpatient and patient satisfaction with tangible, reliability, responsiveness, assurance and empathy variables

Table 3 shows the significant value of Sig. (2-tailed) are tangible variable (p=0.001), reliability variable (p=0.001), responsiveness variable (p=0.001), and assurance variable (p=0.001). This means that there was a significant relationship between the performance of inpatients and patient satisfaction for four variables. However, the significant value of Sig. (2-tailed) was empathy variable (p=0.256). Hence, there was no relationship between the performance of inpatients and patient satisfaction.

Table 3

Correlation test results between inpatient doctor performance and patient satisfaction with 5 variables

No	Variable	R-count value	Sig. (2-tailed)
1	Tangible	0.824	0.000
2	Reliability	0.997	0.000
3	Responsiveness	0.973	0.000
4	Assurance	0.997	0.000
5	Empathy	0.115	0.256

DISCUSSION

This research found that in the survey we conducted all variables have a level of satisfaction is satisfied. There was a correlation between doctors' performance and the level of satisfaction with test results of tangible, reliable, responsiveness, and assurance variables. However, for the empathy variable, there was no correlation. Intangible variable, there were several points, namely the appearance of a clean and tidy doctor, a doctor carrying medical equipment, a clean, tidy, comfortable, and quiet treatment room, and a large hospital building, a strategic location, and adequate parking space (12). From the survey results, several respondents complained that the treatment room was clean, tidy, comfortable, and quiet, especially the bathroom. Many respondents complained that the bathroom was not clean and smelly. To anticipate this, the schedule is to clean the bathroom more often and is written so that the patient and visiting people flush after using the bathroom and do not waste it in the bathroom. In the reliability variable, there are several points namely, doctors come to visit on time, the readiness of doctors to serve patients, doctors act quickly (13). In the results of the survey I conducted, the patient was satisfied with the service at Aisyiyah Siti Fatimah Hospital because all doctors were responsive and fast in providing services. However, some patients were not satisfied with the point that the doctor came to visit on time because patients felt that they did not get a doctor's visit that was not fast enough. This was because the patients still did not know the doctor's schedule.

In the responsiveness variable, there are several points: the doctor always asks the patient's complaints, the doctor allows asking the patient, the doctor gives an explanation about the disease, and when asking the doctor for help, the doctor will immediately come to the room. In this study, the patient was satisfied with the service at the Aisyiyah Siti Fatimah Hospital because the doctor, during a doctor's visit, always asked about the patient's current complaints, allowed him to ask questions, and provide an explanation of the current condition. Patients felt that they were always cared for and made them satisfied. In the assurance variable, there are several points: the doctor's behavior creates a sense of security, the doctor can maintain the patient's confidentiality, and the doctor has the patient's medical record (14). In the survey results, the doctor's behavior that creates a sense of security during the examination will make the patient easily convey their current condition and make them trustworthy. Apart from that, the doctor's attitude of maintaining patient confidentiality allows the patient to tell you everything about the current condition. In the empathy variable, there are several points: the doctor tries to calm the patient's anxiety about the illness, the doctor listens to complaints about the patient's illness and provides solutions in consultation, the doctor provides sufficient service time, the doctor in his service is polite and friendly, and the doctor can guarantee the patient's recovery (5). From the results of this survey, it turns out that patients did not care about doctors who provided services whether they cared or not.

CONCLUSION

There was a significant relationship between doctor's performance and hospitalization with patient satisfaction for tangible variables, reliability, responsiveness, and assurance. There was no relationship between the performance of doctors and hospitalization with patient satisfaction for the variable empathy.

ETHICAL CLEARANCE

Description of ethical exemption is declared to be ethically appropriate in accordance to 7 (seven), with 2011 standards, 1) social values, 2) scientific values, 3) equitable assessment and benefits, 4) risks, 5) persuasion/exploitation, 6) confidentiality and privacy, and 7) informed consent, referring to the 2016 CIOMS guidelines. This is as indicated by the fulfillment of the indicator of each standard.

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Differences in the characteristics of long-term contraceptive device acceptors compared to short-term ones

Diferencias en las características de los aceptores de dispositivos anticonceptivos a largo plazo en comparación con los aceptores a corto plazo

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SUMMARY

Introduction: *Long-term contraception is expected to reduce the Total Fertility Rate. However, currently, the use of short-term contraception is more dominant than the long-term (4:1). The study aims to identify differences in the characteristics of sexually active women of reproductive age using long-term versus short-term contraception.*
Methods: *This study used a descriptive-analytical cross-sectional with a non-random sampling quota using a questionnaire at Mulyorejo Health Center, Indonesia. The data used were primary data regarding age, work status, education level, income level, number of children, husband's support, and knowledge of acceptors or respondents using a research instrument in the form of a questionnaire.*
Results: *Among 130 respondents, 65 respondents were short-term users (50%) and 65 long-term users (50%). Intra-Uterine Device (IUD) is the most preferred long-term contraception because it is non-hormonal, while the injection is the most short-term contraception for practical reasons not to forget, most respondents were <35 years old, did not work, had children aged 2 years, and received support from their husbands in contraception. From the Chi-Square analysis, age (p= 0.001), education level (p= 0.001), and the number of children (p= 0.012) were the distinguishing factors for short-term and long-term contraception use.*
Conclusion: *There are differences in the characteristics of age, education level, and the number of children in sexually active women of reproductive age using long-term and short-term contraception.*

Keywords: *Contraception, characteristics of contraceptive acceptors.*

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RESUMEN

Introducción: *Se espera que la anticoncepción a largo plazo reduzca la tasa de fertilidad total. Sin embargo, actualmente, el uso de anticonceptivos a corto plazo es más dominante que el de largo plazo (4:1). El estudio tiene como objetivo identificar las diferencias en las características de las mujeres sexualmente activas en edad reproductiva que usan anticoncepción a largo plazo versus a corto plazo.*
Métodos: *Este estudio utilizó un corte transversal descriptivo-analítico con una cuota de muestreo no aleatorio utilizando un cuestionario en el Centro de Salud de Mulyorejo, Indonesia. Los datos utilizados fueron datos primarios sobre edad, situación laboral, nivel de educación, nivel de ingresos, número de hijos, apoyo del marido y conocimiento de los aceptantes o encuestados que utilizan un instrumento de investigación en forma de cuestionario.*
Resultados: *Entre 130 encuestados, 65 encuestados eran usuarios a corto plazo (50 %) y 65 usuarios a largo plazo (50 %). El dispositivo intrauterino (DIU) es el método anticonceptivo a largo plazo más preferido porque no es hormonal, mientras que la inyección es el método anticonceptivo a corto plazo por razones prácticas para no olvidar, la mayoría de las encuestadas tenían <35 años, no funcionó, tuvieron hijos de 2 años y recibieron apoyo de sus maridos en anticoncepción. A partir del análisis de Chi-cuadrado, la edad (p= 0,001), el nivel de educación (p= 0,001) y el número de hijos (p= 0,012) fueron los factores que distinguen el uso de anticonceptivos a corto y largo plazo.*
Conclusión: *Existen diferencias en las características de edad, nivel educativo y número de hijos en mujeres sexualmente activas en edad reproductiva que utilizan anticonceptivos a largo y corto plazo.*

Palabras clave: *Anticoncepción, características de los aceptadores de anticonceptivos.*

INTRODUCTION

The problem of increasing Indonesia's population cannot be resolved. The Total Fertility Rate (TFR) of 2.6 from 2002 to 2012 has not decreased. In 2017 it was 2.4, while the 2020 Badan Kependudukan dan Keluarga Berencana Nasional (BKKBN) target was 2.1 (1,2). The problem of the increased population cannot be resolved us caused by a high risk of maternal mortality, the risk of babies dying, and a high poverty rate, according to data from the Badan Pusat Statistik (BPS) 2017, stating that in 2010 and 2012 there was an increase in cases of infants dying from 26 cases to 34 cases, and automatically, the risk of maternal death will also be high. Mother's death will not occur without a pregnancy (3).

Contraception is one way to reduce the risk of increasing the population. However, in Indonesia, the use of contraception among married women aged 15-49 years has continued to decrease from 2013 to 2017, starting from 61.98 to 58.70 (4). A significant increase in contraception use, an increase in age at first marriage, and several socio-economic and cultural factors affect decreasing fertility in Indonesia. In addition, residence (urban or rural), education, access to information, and visits by officers influence women in choosing the contraceptive device (2).

Contraception has two categories, that is long-term contraception to delay, pausing pregnancy, stopping fertility is used for an extended period of at least three years of use in one period of use and not long-term, or short-term contraception is a contraceptive used for a maximum of fewer than three years within one period of use or needing time to change contraceptions. Hence, it can be concluded that long-term contraception has long-term effectiveness so that it is affordable, does not have an effect on breast milk, does not change sexual function, and prevents the risk of maternal death during childbirth (5).

In Indonesia, according to the Indonesian Ministry of Health (2014), there are 8 500 247 couples of reproductive age using contraception. Contraception has several types, and the percentage of contraception use in 2014 was 658 632 Intra-Uterine Device (IUD), 128 795 Female Operation Methods, 21 374 Male Operation Methods, 517 638 condoms, 784 218 implants, 4 128 115 injections, and 2 261 birth control pills. It can be concluded that there are 1:4 users of long-term contraception compared to short-term (6).

There has not been any research on differences in the characteristics of users or contraceptive acceptors. This research needs to be conducted because of the lack of knowledge on the need for sexually active women of reproductive age in contraception choices so that some characteristics of contraception users can be used as a reference

for the government in providing counseling on contraception selection. The awareness of long-term contraception use in Indonesia is still minimal increase the use of the Long Term Contraception Method (MKJP) (6,7). One program of the BKKBN's efforts to reduce the maternal mortality rate is to increase the use of MKJP contraception. In Indonesia, there are types of contraception which hormonal and non-hormonal. Long-term contraception (non-hormonal) includes the implant, IUD, Female Operating Method (MOW), and Male Contraception Method (MOP) (8,9). Injection contraception (hormonal) is the most widely used short-term contraceptive method by married women aged 15-49 years old. Injection contraception remains as a contraceptive method with the highest interest due to its wide variations, high effectiveness, easy access, and invasive risk, It is available in 2 types marketed in Indonesia (2,10). This study aims to identify differences in the characteristics of sexually active women of reproductive age using long-term and short-term contraception.

METHODS

This research is a descriptive-analytic cross-sectional study. This study was chosen because it used a periodic review to prove the differences between long-term and short-term family planning characteristics. This research was carried out from October to December 2019. The samples were women of reproductive age who were sexually active and used contraception within the scope of the Mulyorejo Health Center or were currently at the Mulyorejo Health Center in Jl. Mulyorejo Utara No. 201 City of Surabaya, East Java, Indonesia at the time of research and were willing to be researched. Sampling was done using a non-random sampling quota.

Data collection was carried out using primary data regarding age, work status, education level, income level, number of children, husband's support, and the knowledge of acceptors or respondents using a research instrument in the form of a questionnaire with 65 long-term contraception respondents and 65 short-term contraception respondents. Descriptive and analytical data analysis was used. Descriptively, the data are presented through a frequency table in the form of absolute numbers and bivariate percentages through the Chi-Square test. This research had been registered in the ethics committee of the University of Muhammadiyah Surabaya, Indonesia, with the license number 0764.4/SER/11.3AU/A/2019.

RESULTS

Characteristics of respondents by types of contraception

Table 1 shows that short-term contraceptive acceptors are 65 respondents consisting of respondents who used injections and pills (p= 0.001). While the acceptors of long-term contraception were 65 respondents consisting of respondents who used the IUD, MOW, and implant (p= 0.001).

Table 1

Characteristics of respondents by type of contraception

Contraception	Type	Frequency	Percentage	p
Long-term	IUD	37	56.9	0.000 *
	MOW	12	18.5	
	Implant	16	24.6	
	Total	65	100.0	
Short-term	Injection	47	72.3	0.000 *
	Pill	18	27.7	
	Total	65	100.0	

IUD = Intra-Uterine Device
MOW = Female Operating Method

Based on Table 2, the characteristics of respondents that have a significant difference are age (p=0.001), working status (p=0.001), number of children (p = 0.023) and husband's support (p= 0.001). Meanwhile, other characteristics such as level of education (p= 0.599) and income level (p= 0.161) had no significant differences.

Table 2

The characteristics of 130 respondents

Factor	Category	Frequency	%	p
Age	≤35	100	76.9	0.000 *
	> 35	30	23.1	
Working Status	Work	44	33.8	0.000 *
	Does not work	86	66.2	
Level of education	Basic	62	47.7	0.599
	Higher	68	52.3	
Income	< Minimum wage	73	56.2	0.161
	≥ Minimum wage	57	43.8	
Number of children	≤2	78	60.0	0.023 *
	> 2	52	40.0	
Husband's Support	Supported	127	97.7	0.000 *
	Not supported	3	2.3	

Based on Table 3, there is a significant difference of 0.035 on long-term acceptors and a significant difference of 0.001 in short-term acceptors who are ≤ 35 years old and > 35 years old. There was a significant difference of 0.018 long-term acceptors and a significant difference of 0.004 short-term contraceptive acceptors who did not work. There was a significant difference of 0.002 for long-term acceptors and 0.018 for short-term acceptors with basic education and higher education. At the income level, there was no significant difference of 0.172 for long-term acceptors, and there was no significant difference of 0.525 in the short term with income < minimum wage and ≥ minimum wage. In the number of children, there was no significant

Table 3

Characteristics of Respondents of Long-Term and Short-Term Contraception

Factor	Category	Long-term		P	Short-term		p
		frequency	%		frequency	%	
Age	≤35	41	63.1	0.035 *	59	90.8	0.001 *
	> 35	24	36.9		6	9.2	
Working Status	Work	23	35.4	0.018 *	21	32.3	0.004 *
	Does not work	42	64.6		44	67.7	
Level of education	Basic	20	30.8	0.002 *	42	64.6	0.018 *
	Higher	45	69.2		23	35.4	
Income	< Minimum wage	38	58.5	0.172	35	53.8	0.525
	≥ Minimum wage	27	41.5		30	46.2	
Number of children	≤2	32	49.2	0.901	46	70.8	0.001 *
	> 2	33	50.8		19	29.2	
Husband's Support	Supported	64	98.5	0.000 *	63	96.9	0.000 *
	Not supported	1	1.5		2	3.1	

difference of 0.901 in long-term acceptors, and there was a significant difference of 0.001 in the short-term acceptors having children ≤ 2 with > 2. In the husband's support, there was a significant difference of 0.001 for long-term acceptors and a significant difference of 0.000 for short-term acceptors supported by their husbands and those without their husbands' support.

Based on Table 4, the respondents aged >35 years tend to use long-term contraception 5.75 times higher than respondents aged ≤35 years (p= 0.001). It indicates that age can affect the choice of contraception. There was no difference in 0.711 characteristics of long-term and short-term contraceptive acceptors based on work status, showing that work status does not affect the choice of contraception. Respondents with basic education to use long-term contraception were 4.11 times higher than respondents with higher education (p= 0.001), indicating that the level of education affects the choice of contraception. There was no difference in 0.596 characteristics of long-term and short-term contraceptive acceptors based on family income. Hence, family income does not affect the choice of contraception. Respondents with children >2 tended to use long-term contraception 2.49 times higher than respondents with children ≤2 (p= 0.012) so that the number of children affects the choice of contraception. There was no difference in 0.559 characteristics which shows relatively homogeneous characteristics of long-term and short-term contraceptive acceptors based on the husband's support.

Table 4

Differences characteristics of long-term and short-term contraceptive acceptors

Factor	Category	Long-term		Short-term		p	OR
		frequency	%	frequency	%		
Age	≤35	41	63.1	59	90.8	0.000 *	5.75
	> 35	24	36.9	6	9.2		
Working Status	Work	23	35.4	21	32.3	0.711	1.147
	Does not work	42	64.6	44	67.7		
Level of education	Basic	20	30.8	42	64.6	0.000 *	4.11
	Higher	45	69.2	23	35.4		
Income	<Minimum wage	38	58.5	35	53.8	0.596	1.26
	≥Minimum wage	27	41.5	30	46.2		
Number of children	≤2	32	49.2	46	70.8	0.012 *	2.49
	> 2	33	50.8	19	29.2		
Husband's Support	Supported	64	98.5	63	96.9	0.559	2.032
	Not supported	1	1.5	2	3.1		

OR = Odds Ratio

DISCUSSION

Several characteristics of the respondents have significant differences in the use of long-term and short-term contraception, including age, level of education, and the number of children. These factors affect the choice of contraception in sexually active women of reproductive age. At the age of ≤35 years old they use short-term contraception because they want to space out pregnancies and still want to increase the number of children, while those who aged >35 years prefer to use long-term contraception because they want to stop increasing the number of children; it practically can be used for at least three years. There were significant differences between long-term and short-term contraceptive acceptors based on age, indicating that age affects the choice of contraception. The research reinforces that the majority of women over 30 years of age use long-term contraception so that age affects the choice of contraception (11).

The majority of short-term contraceptive acceptors were basic school education, while most long-term contraceptive acceptors had high school education. There are significant differences between long-term and short-term contraceptive acceptors based on education so that education affects the choice of contraceptive type. In line with research, there is a significant relationship between the decision to choose contraception to the level of education. The higher the level of education, the more rational it is to choose contraception (11). The level of education affects the choice of contraception because someone who has higher education, in general, will have a broader view and more easily accept innovative ideas and things (12). Thus, the level of education can be used as a factor in choosing contraception.

Respondents dominated long-term contraceptive acceptors with children >2, while short-term contraceptive acceptors were dominated by respondents who had children <2. There were significant differences between long-term and short-term contraceptive acceptors based on the number of children. It is in line with research which states that there is a significant relationship with the number of children or parity of contraceptive acceptors in determining decisions; acceptors with parity of more than 2 children are ten times more likely to choose long-term contraception than parity with less than two children (13). In contrast, another study states that there is no relationship between the number of children and the use of contraception (14).

Short-term contraceptive acceptors were dominated by women who did not work. There was homogeneity of long-term and short-term contraceptive acceptors based on work status so that work status does not affect the choice of contraception type. It is in line with the research which states that work status has no relationship with the choice of contraception because contraceptive acceptors will not interfere with work activities even when using contraception (15). In contrast which states that working women prefer long-term contraception because they are practical, safe, and have long-term effects (12).

Both long-term and short-term contraceptive acceptors had family income < minimum wage. There was no significant difference between long-term and short-term contraceptive acceptors based on income. It is reinforced by a study stating that income does not affect someone using the contraceptive method (16). Meanwhile, high family income has a 4.8 times chance of using long-term contraception compared to low family income (17).

Both long-term and short-term contraceptive acceptors received support from their husbands. There was no significant difference between long-term and short-term contraceptive acceptors based on the husband's support. In line with research which states that partner support has a relationship with the choice of contraception (8).

CONCLUSION

Factors that influence the choice of long-term or short-term contraception are age, education level, number of children. Factors that do not affect the choice of long-term or short-term contraception are factors of work status, income, and husband's support. The result of the study explained that there were differences in the characteristics of age, education level, and the number of children in sexually active women of reproductive age using long-term and short-term contraceptive.

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Conflicts of Interest

There is no conflict of interest in the research.

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Factors associated with the success of exclusive breastfeeding in the rural area

Factores asociados al éxito de la lactancia materna exclusiva en el área rural

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SUMMARY

Introduction: *In Indonesia, coverage of exclusive breastfeeding has not yet met the government's goal of 80 %. This study aimed to ascertain the relationship between maternal education and occupation, family support, and belief in myths and exclusive breastfeeding success in a rural region.*
Methods: *This cross-sectional study was conducted in the Mentoro Village, Indonesia, from October 2020 to December 2020. The data collection was carried out using a questionnaire.*
Results: *Among 50 respondents, the age of breastfeeding mothers at the age of 20-29 and 30-39 years old was the same. Most of the respondents graduated from university (78 %), 29 mothers were housewives (58 %), mothers obtained support from family (90 %), and mothers believed in myths (82 %). Variables associated with the exclusive breastfeeding success were education level (p= 0.019), maternal occupation (p= 0.025), family support (p= 0.006), and belief in myths (p= 0.042). The occupation and family support were risk factors for the success of exclusive breastfeeding (p= 0.014; p= 0.045, respectively).*
Conclusion: *Maternal education level and occupation, family support, and belief in myths were associated with the success of exclusive breastfeeding.*

Keywords: *Exclusive breastfeeding, education level, occupation, family support, myths belief, rural area.*

RESUMEN

Introducción: *En Indonesia, la cobertura de la lactancia materna exclusiva aún no ha cumplido la meta del gobierno del 80 %. El objetivo de este estudio fue determinar la relación entre la educación y la ocupación materna, el apoyo familiar y la creencia en los mitos y el éxito de la lactancia materna exclusiva*

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en una región rural.
Métodos: *Este estudio transversal se realizó en Mentoro Village, Indonesia, de octubre de 2020 a diciembre de 2020. La recolección de datos se realizó mediante un cuestionario.*
Resultados: *Entre los 50 encuestados, la edad de las madres que amamantaban entre los 20 y 29 años y entre los 30 y 39 años era la misma. La mayoría de los encuestados se graduaron de la universidad (78 %), 29 madres eran amas de casa (58 %), las madres obtuvieron apoyo de la familia (90 %) y las madres creían en los mitos (82 %). Las variables asociadas al éxito de la lactancia materna exclusiva fueron el nivel educativo (p= 0,019), la ocupación materna (p= 0,025), el apoyo familiar (p= 0,006) y la creencia en mitos (p= 0,042). La ocupación y el apoyo familiar fueron factores de riesgo para el éxito de la lactancia materna exclusiva (p= 0,014; p= 0,045, respectivamente).*
Conclusión: *El nivel de educación y ocupación materna, el apoyo familiar y la creencia en los mitos se asociaron con el éxito de la lactancia materna exclusiva.*

Palabras clave: *Lactancia materna exclusiva, nivel de educación, ocupación, apoyo familiar, mitos creencia, área rural.*

INTRODUCTION

Breastfeeding exclusively for six months and continuing for up to two years is the optimal nutrition for infants (1). Breastfeeding protects children from life-threatening and chronic illnesses. It also supports the early development of children and is associated with their higher intelligence. Globally, improving breastfeeding rates has the potential to save the lives of over 820 000 children under the age of five (2). Infants aged 0 to 6 months need sufficient nutrition from exclusive breastfeeding. The nutritional requirement fulfillment of the baby who is not given exclusive breastfeeding is not optimal, and the nutritional status is impaired (3). Exclusive breastfeeding supports optimal growth so that the incidence of malnutrition can decrease. The incidence of malnutrition is lower in children who receive exclusive breastfeeding than those who do not receive exclusive breastfeeding (4).

United Nations Children's Fund (UNICEF) Indonesia states that from 5 million children born each year in Indonesia, more than half do not get breast milk optimally in their first year of life (5). The coverage of breastfeeding in Indonesia in 2016 did not reach the target set by the government. According to data in 2007 - 2013, the prevalence of exclusive breastfeeding in Indonesia was decreased from 32 % to 30.2 %. Data obtained from the Provincial Health Office of East Java showed that the coverage of exclusively breastfed infants in East Java in 2016 was 74 %. Overall achievement in East Java had not met the predetermined target of 80 % (6). This phenomenon indicates that many mothers in Indonesia are rarely giving exclusive breastfeeding. In Indonesia, exclusive breastfeeding is governed by a statute, which specifies that every child, except for medical indications, has the right to receive exclusive breastfeeding for six months from birth (7).

Breastfeeding exclusively can help reduce child mortality. Indonesia has a poor rate of exclusive breastfeeding (8,9). Numerous factors, including cultural factors, affected exclusive breastfeeding practices in developing countries. There are many myths and cultural beliefs among the community regarding breastfeeding and influenced the success of exclusive breastfeeding activities in developing countries (10). However, there are still limited data in Indonesia, especially from the rural area. This study aims to determine whether the belief in the myths spread in the community about breastfeeding and other factors such as the level of mother's education, mother's occupation, and support from family could influence exclusive breastfeeding in Mentoro Village, East Java, Indonesia.

METHODS

This cross-sectional study was conducted in the Mentoro Village Area, East Java Province, Indonesia, from October 2020 to December 2020. The population of this study was breastfeeding mothers who had babies aged more than six months. The sampling technique used a simple random sampling technique. The sample obtained in this study was 50 breastfeeding mothers. This research was approved by the Health Research Ethics Commission of the Muhammadiyah University of Surabaya, Surabaya, Indonesia (No certificate: 051. /KET./11.3./AU./F/2020).

In this study, the data collection technique used a questionnaire by google form link given to breastfeeding mothers by visiting each house according to the data provided. In the pandemic Corona Virus Disease 2019 (COVID-19), researchers could not gather all the respondents in one place simultaneously. The data were analyzed using the chi-square test by Statistical Product and Service Solutions (SPSS) application. The researchers' questionnaire referred to previous existing questionnaires, then supplemented by various myths spread in the research area and tested for validity and reliability.

RESULTS

Characteristics of breastfeeding mothers

Based on Table 1, the age of breastfeeding mothers at the age of 20-29 years old and 30-39 years old is the same. Most of the respondents who graduated from university for the latest education were 39 mothers (78 %). Most of the respondents' occupation was 29 mothers as housewives (58 %). Among 50 respondents, there were 45 mothers with obtained support family (90 %). For the myth belief, it is known that most of the respondents were 41 mothers who believed (82 %).

Table 1

The distribution of breastfeeding mother characteristics in Mentoro Village, Sumobito District, Jombang Regency, Indonesia

Characteristics	Category	Frequency	Percentage
Age (year)	20 – 29	25	50
	30 – 39	25	50
Level of Education	High School	11	22
	University	39	78
Occupation	Government employees	2	4
	Private Employees	10	20
	Entrepreneurs	9	18
	Housewives	29	58
Family Support	Without Family Support	5	10
	Obtained family support	45	90
Myths Belief	Do not believe	9	18
	Believe	41	82
Total		50 mothers	100

The relationship between education level, occupation, family support and myth belief with the success of exclusive breastfeeding

All data had been tested by Chi-square since it meets the requirements of the chi-square test to determine the relationship between the influencing factors and the success of exclusive breastfeeding. Based on Table 2, it can be seen the test results of maternal education level (p= 0.019), maternal occupation (p= 0.025), family support (p= 0.006) and belief in myth (p= 0.042) had significant relationship with the success of exclusive breastfeeding.

Multivariate analysis

Table 3 shows that the statistical test results of the occupation variable are p-value 0.014 (p< 0.05) with a prevalence ratio of 11 (95 % CI 1.633 - 74.083). The family support variable showed a p-value of 0.010 (p< 0.05) and a prevalence ratio of 0.045 (95 % CI 0.004 - 0.480). The range of confidence intervals on these two variables does not include number 1, which indicates that the variables of work and family support are risk factors for the success of exclusive breastfeeding.

Table 2

Table cross relationship between maternal education level and the success of exclusive breastfeeding

Characteristics	Category	The success of exclusive breastfeeding				p
		Without exclusive breastfeeding		Exclusive breastfeeding		
		n	%	n	%	
Education Level	Low Education	13	38.2	21	61.8	0.019
	High Education	1	6.2	15	93.8	
Occupation	Unemployed	10	22.7	34	77.3	0.025
	Employed	4	66.7	2	33.3	
Family Support	Without family support	4	80.0	1	20.0	0.006
	Obtained Family Support	10	22.2	35	77.8	
Belief Myth	Unbelieve Myth	5	55.6	4	44.4	0.042
	Believe	9	22.0	32	78.0	

Table 3

Results of multivariate analysis of maternal education and occupation levels, family support and belief in the myth towards the success of exclusive breastfeeding in Mentoro Village, Sumobito District, Jombang Regency, Indonesia

	Variable	Coefficient	p	RP (CI 95%)
Step 1	Education Level	-2.700	0.051	0.067 (0.004-1.010)
	Occupation	2.454	0.029	11.64 (1.280-105.873)
	Family Support	-2.786	0.043	0.062 (0.004-0.919)
	Constant	1.703	0.282	5.489
Step 2	Occupation	2.398	0.014	11 (1.633-74.083)
	Family Support	3.091	0.010	0.045 (0.004-0.480)
	Constant	-693	0.423	0.5

DISCUSSION

Breastfeeding is both a natural situation and an art that must be re-learned. Breastfeeding provides opportunities for babies to benefit from growing physically healthy, getting intelligence and emotional stability, and improving positive social and spiritual (11). Breastfeeding from the first day of birth can reduce the risk of death for newborns by 45 % (12). The success and failure of exclusive breastfeeding are influenced by several factors, including education level, knowledge, attitudes, experiences of mothers, number of children, pregnancy examinations, and early breastfeeding. The factors that can trigger childbirth assistance are efforts to prepare for exclusive breastfeeding, family support, health worker support, husband support, and formula milk advertisements (13).

Most of the breastfeeding mothers in Mentoro Village are indigenous people who live in the

village. Mentoro Village is one of the villages in Sumobito District, Jombang Regency, East Java Province, Indonesia. The area of agricultural land in Mentoro Village exceeds half of the village area because most of the villagers live as farmers. Most of the breastfeeding mothers are housewives and some occupied as kindergarten and elementary school teachers in the village, and most of their husbands work as farmers.

Education level also affects the knowledge level, while knowledge plays an essential role in changing attitudes and behavior; the higher a person's education level, the broader understanding's ability to accept new positive behavior (14). Mothers who have high education levels are easier to understand and choose exclusive breastfeeding for 6 months. They also assume that breast milk is the perfect baby food during the first 6 months. From this study, 26 % of breastfeeding mothers who did not exclusively breastfeed with recent low education tended to experience major breast milk production obstacles. Low education mothers usually provide additional food or other drinks for newborn babies, such as water, honey, bananas, and formula milk. Another study from Poland also showed that knowledge of general breastfeeding was a strong predictor for exclusive breastfeeding. Also, increasing breastfeeding knowledge could improve successful breastfeeding rates (15).

The reason women have to work outside their homes is because of economic demands. This condition forced them to leave their babies with other family members or caregivers, and thus, their babies were only fed by formula milk (6). For mothers who work every day, the obstacles they experience are due to the short time for maternity and childbirth leave and the lack of knowledge and information about breastfeeding babies, which is an obstacle for mothers who do not exclusively breastfeed (16). Additionally, another study conducted in Iran discovered that housewives had a longer period of exclusive breastfeeding than working mothers (17).

From the respondents' various opinions, most of them are exclusively breastfed and housewives, who only take care of their children and work in the kitchen daily to have more time with their children. Working mothers often entrust their babies to parents or parents-in-law and their families. Usually, they failed to give exclusive breastfeeding to their babies. Based on the analysis result, the occupational risk increases 0.14 times for exclusive breastfeeding success. Additionally, this research demonstrates an important relationship between work and exclusive breastfeeding success.

Family support becomes something that mothers highly require in taking care of their babies. Family support can be obtained from the husband, parents, in-laws, or other families. Suppose the family always motivates and supports the mother. In that case, this affects the mother's behavior and attitudes so that she is encouraged to take action according to what is expected and with the intention, self-confidence, and belief in the mother vice versa (18). The study from Bangladesh showed that the role of husband support is crucial for the breastfeeding mom. They showed that intimate partner violence is associated with more inadequate breastfeeding practices in Bangladesh (19).

Types of family support listed in this study's questionnaire are emotional support provided by the family, such as attention by asking about the mother and baby, listening to the mother's complaints and problems during breastfeeding. Afterward, family support ensures mothers give breast milk to babies. Praise support to the mothers that had given breast milk. Considering that praise means giving an appreciation to the mothers who can give full breastfeeding to the baby. Instrumental support includes helping mothers look after and bathe the baby, assisting in housework for mothers, providing nutritious food for mothers during breastfeeding. All these supports can ease the burden on mothers to provide breast milk to their babies. The previous study from China also showed a higher prevalence of exclusive breastfeeding among mothers who got support from their partners (20).

This study's results are in line with the research conducted, which states that the report on the results of the analysis of the relationship between family support and self-confidence in exclusive breastfeeding with the chi-square test shows the relationship between family support and increased exclusive breastfeeding. On the contrary, some myths support exclusive breastfeeding (21). The myths in this research questionnaire include

positive and negative myths. Examples of positive breastfeeding myths are mothers who breastfeed not consuming alcohol and mothers with small breast sizes produce less milk than mothers with larger breasts. In contrast, examples of negative myths are mothers who eat spicy food will lead eye boogers to the baby and mothers who do not consume herbal (ginger, turmeric, galanga) have fishy breast milk.

Respondents' responses in questionnaires indicate they believed in negative myths such as mothers who eat spicy food will lead eye boogers to the baby and mothers who do not consume herbal (ginger, turmeric, galanga) have fishy breast milk. Most mothers have believed in the myth about breastfeeding that has been passed down from generation to generation from their parents. It has been applied for a long time, and most of the population living in the village still has a strong belief in hereditary culture.

CONCLUSION

Several factors may influence exclusive breastfeeding in rural areas. This research shows a significant relationship of education level, maternal work, family support, and belief in myth towards the success of exclusive breastfeeding in the Mentoro Village, Indonesia. Increasing family support and giving general knowledge about breastfeeding may improve the success of exclusive breastfeeding rates.

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Admission assessment criteria in predicting students' academic performance in newly established medical school

Criterios de evaluación de admisión para predecir el rendimiento académico de los estudiantes en la facultad de medicina recientemente establecida

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SUMMARY

Introduction: *Various medical education institutions around the world have different methods and criteria in selecting the ideal candidate. This study aims to determine the most appropriate admission criteria for predicting student academic performance in a newly established medical faculty in Indonesia.*
Methods: *In this cross-sectional study, we collected admission and academic performance data from 140 students admitted in 2016, 2017, and 2019. Data included academic ability test results, psychological test recommendation, and Intelligence Quotient (IQ) during admission.*
Results: *There was a significant correlation between students' academic ability test results and IQ with academic performance ($p<0.05$), with a very weak level of correlation ($r= 0.1888$ and $r= 0.278$, respectively). On the other hand, there was no significant correlation between the students' psychological test recommendations and academic performance. IQ affected 22.7 % of student academic performance, and the academic ability test results and IQ, simultaneously, affected academic performance ($p<0.05$), as much as 5.4 %.*
Conclusion: *Intelligent quotients were the most capable of predicting students' academic performance in the admissions process to evaluate medical students' cognitive and non-cognitive aspects.*

Keyword: *Assessment criteria, IQ, students' academic performance.*

RESUMEN

Introducción: *Varias instituciones de educación médica de todo el mundo tienen diferentes métodos y criterios para seleccionar al candidato ideal. Este estudio tiene como objetivo determinar los criterios de*

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admisión más apropiados para predecir el rendimiento académico de los estudiantes en una facultad de medicina recientemente establecida en Indonesia.
Métodos: *En este estudio transversal, recolectamos datos de admisión y rendimiento académico de 140 estudiantes admitidos en 2016, 2017 y 2019. Los datos incluyeron resultados de pruebas de capacidad académica, recomendación de pruebas psicológicas y Cociente de Inteligencia (CI) durante la admisión.*
Resultados: *Hubo una correlación significativa entre los resultados de las pruebas de capacidad académica de los estudiantes y el coeficiente intelectual con el rendimiento académico ($p<0.05$), con un nivel de correlación muy débil ($r= 0.1888$ $yr= 0.278$, respectivamente). Por otro lado, no hubo una correlación significativa entre las recomendaciones de las pruebas psicológicas de los estudiantes y el rendimiento académico. El coeficiente intelectual afectó el 22,7% del rendimiento académico de los estudiantes, y los resultados de las pruebas de capacidad académica y el coeficiente intelectual, simultáneamente, afectaron el rendimiento académico ($p<0,05$), hasta un 5,4%.*
Conclusión: *Los cocientes inteligentes fueron los más capaces de predecir el rendimiento académico de los estudiantes en el proceso de admisión para evaluar los aspectos cognitivos y no cognitivos de los estudiantes de medicina.*

Palabras clave: *Criterios de evaluación, coeficiente intelectual, rendimiento académico de los estudiantes.*

INTRODUCTION

Students are referred to as intellectual candidates or students who can improve their achievement in society are known as agents of change (1). The study program on health is indeed the most popular study program when entering university (2). The Faculty of Medicine is in great demand by the wider community. Therefore, a valid admission selection mechanism is needed to acquire a good quality of student input (3). The admission selection is generally carried out by assessing cognitive and non-cognitive aspects. In the cognitive aspect, conventionally, pre-admission assessments aim to cover academic and non-academic cognitive variables (4). Cognitive tests are needed to assess problem-solving skills, which are often reflected in intellectual abilities, performance on exams recalling factual information or memory, and language skill tests (5). The non-cognitive aspects of the selection of new students are expected to assess 'non-cognitive' or personal qualities, including features, such as personality attributes, attitudes, interests, values, and other personal characteristics (6,7).

Various medical education institutions worldwide have different methods and criteria in selecting the ideal candidate, including cognitive and non-cognitive criteria (8). Academic performance is a criterion for assessing success in education (9). The tests carried out are expected to predict student academic performance or outcomes during the education period. If the test carried out has been a good predictor, the student input obtained will also be of higher quality, and the learning process can run smoothly (10). However, choosing the criteria of admission selection that has proven valid as a predictor of student academic performance is not easy. Several universities' research gives different predictive validity test results. There is a predictive validity of academic tests on the admission process in academic achievement, whereas the psychological characteristics have no significant association with the academic achievement (11). However, on the other hand, a cohort study in health colleges showed that cognitive ability tests at admission and previous academic performance did not predict student academic performance (12). The medical program's psychometric and psychological method also has good predictive validity (13).

The medical doctor profession itself requires three components of ability: a combination of three essential elements of medical knowledge, procedural or technical skills, and personality that contribute to physicians' performance in training and physicians' practice (6). The admission selection implemented should be able to filter students with the right qualifications in these three aspects. Regardless of the selected admission criteria, maintaining competitiveness in selecting new students poses a significant challenge for newly established medical institutions, where the number of applicants for new student candidates is still lacking (14). Therefore, there was a need for appropriate methods and criteria to get qualified and competitive student input yet still meeting the available quota. Based on this description, a study is needed to analyze how the predictive validity of the admission selection criteria affects

medical students' academic performance. This study aims to determine the most appropriate admission criteria for predicting student academic performance in a newly established medical faculty in Indonesia.

METHODS

We conducted this analytic observational research with a cross-sectional design at the Faculty of Medicine, Universitas Muhammadiyah Surabaya, Indonesia, from January to March 2021. The population in this study were students admitted in 2016, 2017, and 2018. We collected 140 students that met the inclusion criteria, namely students who were active and had complete data. The minimum sample size used in this study is calculated based on the cross-sectional research formula:

$$n = \frac{Z^2_{1-\alpha/2}\, p\,(1-p)\, N}{d^2(N-1) + Z^2_{1-\alpha/2}\, p\,(1-p)}$$

Based on the formula above, the minimum sample is 109. The sampling technique was carried out by the consecutive sampling method.

Collected data included student characteristics such as sex, high school origin, age, and year of admission; admission criteria selection for new students, namely academic ability test results, psychological test recommendations, and IQ; and academic performance indicator, which is the GPA. Academic performance was obtained from student achievement index data in the second year.

This research procedure was carried out by first making a proposal and arranging permits. The required ethical approval was obtained from the Komite Etik Penelitian Kesehatan (KEPK), Universitas Muhammadiyah Surabaya, Indonesia. To ensure confidentiality, the primary researcher coded the data in line with the institutional ethical guideline. The data obtained were then analyzed using the Statistical Package for the Social Sciences (SPSS) version 26 application using the correlation test and continued with the linear regression test if the significant results founded.

RESULTS

Table 1 shows that most of the respondent is females (63 %), comes from a public school (67 %), the majority is 18 years old (46 %), and the majority of student admissions is in 2016 (35.7 %).

Table 1

Characteristics of research subjects

Characteristics		N	%
Sex	Males	52	37
	Females	88	63
High school origin	Public school	94	67
	Private school	46	33
Age during admission (year)	16	3	2
	17	33	24
	18	65	46
	19	24	17
	20	9	6
	21	4	3
	22	1	1
	24	1	1
Year of admission	2016	50	35.7
	2017	44	31.4
	2018	46	32.9

Table 2 shows that there is a significant correlation between students' academic ability test results and IQ with academic performance ($p<0.05$), with a very weak level of correlation ($r= 0.1888$ and $r= 0.278$, respectively). On the other hand, there was no significant correlation between the students' psychological test recommendations and academic performance.

Table 2

Results of the Spearman Correlation Test Analysis

Variable	Academic performance (second year cGPA)
Academic ability test results	r = 0.188 P < 0.05* n = 140
Psychological test recommendations	r = 0.062 P > 0.464 n = 140
IQ	r = 0.278 P < 0.05* n = 140

* shows significant result
cGPA = cumulative Grade Point Average; IQ = Intelligent Quotients

The linear regression test was then carried out to the significant results. Table 3 shows the results of the linear regression test between the academic ability test results and the IQ on student academic performance. It is found that IQ affected academic performance where the correlation coefficient value was 0.227, indicating that IQ affects 22.7 % of student academic performance by itself ($p<0.05$). Meanwhile, academic ability test scores did not affect GPA.

The linear regression test between the academic ability test and IQ simultaneously on students' academic performance based on the test seen in Table 3 shows that the results of the academic ability test and IQ simultaneously affect academic performance ($p<0.05$), with a correlation coefficient of 5.4 %.

Table 3

Linear regression test between the academic ability test and IQ on the students' academic performance

Variable	Coefficient correlation R2	p
Academic ability test results	0.039	0.640
IQ	0.227	0.007*

* shows significant result
IQ = Intelligent Quotients

DISCUSSION

The characteristics of the respondents analyzed in this study included sex, age, and high school origin. From the data of 140 students, most of them were female. Female medical students tend to be more competitive, hard workers, and care more about their academic performance (2). The sample age of this study was 16-24 years, with the most significant age being 18 years. The age is far above the average because prospective students have previously studied at other faculties. The data regarding the origin of high schools in our study sample were 67% from public high schools and 33% from private high schools. This data are also following the Indonesian Ministry of Education and Culture, showing that even though many private high schools are emerging, the number of public high schools in Indonesia is still much higher, reaching more than two-fold (15).

The new student admission test is an essential process in screening students who enter a college. In Indonesia, the entrance selection test for private universities is carried out independently through several stages. This selection test was carried out in this study using several criteria, namely academic ability tests, psychological tests, interviews, and physical examinations. The academic ability test consists of 100 questions representing five disciplines (20 questions each): Biology, Chemistry, Physics, Mathematics, and English. This study discusses the effect of academic ability tests, psychological test results, and IQ scores on student academic performance.

The academic ability test, which was carried out on selecting new students, aims to test the participants' cognitive abilities. It contained test questions for academic ability such as

Mathematics, English, Indonesian, and Science questions. There was a correlation between the test of academic ability and student academic performance ($p<0.05$). This study is following the research conducted on 97 respondents in the Medical Faculty of Swadaya Gunung Jati University, which showed that the academic selection test had a significant relationship with the preclinical cumulative GPA (13). Likewise, a study with 116 respondents from Abulyatama Medical Faculty obtained results in establishing a significant relationship between the students' entrance examination results and their GPA (16). Student ability in academic performance achieved can be seen in the GPA (cognitive aspects) (17).

Weak academic ability tests in predicting student academic performance can be seen from the value of the linear regression test, which shows no significant correlation between tests of students' academic ability and academic performance. The basic academic ability test, or what is known as the traditional entrance screening test, is considered to be less able to predict students' ability in the educational process (10,11). However, if this test is carried out correctly, it can be used as a valuable measuring tool because knowledge and skills can predict how the person will learn and develop in the future (18).

The IQ and academic ability test result simultaneously affected academic performance ($p<0.05$), indicating that the cognitive test results are a good and consistent predictor of performance in education. However, because the correlation is still weak, the test's quality and validity need to be reviewed (13). Research conducted in Saudi Arabia explained that cognitive assessment as a student selection could also be assessed with other cognitive parameters. In that study, the most reliable academic assessment in predicting academic performance is the NAT (National Achievement Test) in assessing the cumulative knowledge acquired throughout the final three years of high school in five subjects: Biology, Chemistry, Physics, Mathematics, and English (4). Therefore, during admission selection, the NAT score can be considered one of the criteria for making decisions or as a requirement for passing the preadmission test.

Student academic performance can also be predicted by assessing non-academic cognitive abilities such as the GAT (general aptitude test score). This test aims to measure verbal mastery, quantitative mastery, analytical writing, and students' critical thinking skills through a long-term learning process. Various scientific reports have shown a positive correlation between the GAT and educational scores in various academic programs (11,18,19). In conclusion, it is necessary to consider the GAT in selecting new student admissions besides the academic ability test, considering that in addition to correlating with academic performance. Although they are sometimes viewed as lacking validity and acting as barriers to certain groups of applicants, aptitude tests and academic record are viewed as most useful in the decision of whom to call to interview, and this test is a good predictor of clinical performance needed for medical students (18,20).

Medical education provides demands for students to have noncognitive competencies in addition to cognitive aspects. In this study, the noncognitive aspects of students were assessed by psychological tests. Students' individual characteristics are summarized in a psychogram that provides information about the level of intelligence (IQ), general abilities, abilities and work styles, and personality. One of the challenges for a newly established faculty is poor opportunities for promotion so that the number of applicants is still relatively small (14). The test is carried out only to measure the potential where the manifestation can be influenced by various other things both from within and from outside the student.

CONCLUSIONS

In the admission selection, the selected selection criteria could predict second-year students' academic performance even with a very weak level of correlation. Among all criteria, IQ was the most capable of predicting students' second-year academic performance. The results could indicate the need to reevaluate the admission criteria for our medical faculty because more valid criteria are needed in the admission process to evaluate the cognitive and non-cognitive aspects of medical students.

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Conflicts of Interest

The authors declare no conflict of interest.

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The effect of Ramadan fasting on clinical and laboratory parameters in chronic kidney disease patients underwent hemodialysis

El efecto del ayuno de Ramadán en los parámetros clínicos y de laboratorio en pacientes con enfermedad renal crónica sometidos a hemodiálisis

Langgeng Perdhana[1*•], Shofa Chasani[2*]

SUMMARY

Background: *Despite getting relief from not fasting during Ramadan, some hemodialysis patients will ask questions about how fasting affects their health and whether they are allowed to fast. This study aims to determine the relationship between Ramadan fasting on clinical and laboratory parameters in chronic kidney disease (CKD) patients undergoing hemodialysis.*

Methods: *The cohort design study was carried out from April to May 2020 at the Hemodialysis Unit of Roemani Muhammadiyah Hospital Semarang. The dependent variables included pre-dialysis weight, Inter Dialytic Weight Gain (IDWG), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), hemoglobin level (Hb).*

Result: *Among 33 respondents, it was found that 11 (33.3 %) respondents were fasting during Ramadan, and 22 (66.7 %) respondents were not fasting. The respondents consisted of 17 males (51.5 %) and 16 females (48.5 %). The mean age was 55.4 ± 10.5 years. The duration of hemodialysis was 24 ± 20.1 months. The independent t-test showed a significant relationship between Ramadan fasting and pre-dialysis weight (p=0.003). As for the variables IDWG, SBP, DBP, and Hb, there was an insignificant relationship (p>0.05).*

Conclusion: *Ramadan fasting does not relate to IDWG, SBP, DBP, and Hb level parameters. These results indicate that the condition of hemodialysis patients who are fasting is the same as those who are not fasting, so it is safe if hemodialysis patients wish to fast in Ramadan.*

Keywords: *Chronic kidney disease, hemodialysis, Ramadan fasting.*

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RESUMEN

Antecedentes: *A pesar de sentirse aliviado por no ayunar durante el Ramadán, algunos pacientes en hemodiálisis harán preguntas sobre cómo el ayuno afecta su salud y si se les permite ayunar. Este estudio tiene como objetivo determinar la relación entre el ayuno de Ramadán y los parámetros clínicos y de laboratorio en pacientes con enfermedad renal crónica (ERC) sometidos a hemodiálisis.*
Métodos: *El estudio de diseño de cohortes se llevó a cabo de abril a mayo de 2020 en la Unidad de Hemodiálisis del Hospital Roemani Muhammadiyah Semarang. Las variables dependientes incluyeron el peso previo a la diálisis, el aumento de peso interdiálisis (IDWG), la presión arterial sistólica (PAS), la presión arterial diastólica (PAD), el nivel de hemoglobina (Hb).*
Resultados: *Entre los 33 encuestados, se encontró que 11 (33,3 %) encuestados estaban ayunando durante el Ramadán, y 22 (66,7 %) encuestados no estaban ayunando. Los encuestados fueron 17 hombres (51,5 %) y 16 mujeres (48,5 %). La edad media fue de 55,4 ± 10,5 años. La duración de la hemodiálisis fue de 24 ± 20,1 meses. La prueba t independiente mostró una relación significativa entre el ayuno de Ramadán y el peso previo a la diálisis (p= 0,003). En cuanto a las variables IDWG, PAS, PAD y Hb, hubo una relación no significativa (p> 0,05).*
Conclusión: *El ayuno de Ramadán no se relaciona con los parámetros de nivel de IDWG, PAS, PAD y Hb. Estos resultados indican que la condición de los pacientes en hemodiálisis que están en ayunas es la misma que la de los que no lo hacen, por lo que es seguro si los pacientes en hemodiálisis desean ayunar en Ramadán.*

Palabras clave: *Enfermedad renal crónica, hemodiálisis, ayuno de Ramadán.*

INTRODUCTION

Ramadan, the ninth month of the Muslim lunar calendar (Hijra), represents the holiest month for Muslims. Ramadan's length varies, as the Islamic lunar year is 354 days long and the Ramadan month is 29 or 30 days long. There is an order to fast during the month of Ramadan, which is one of Islam's five pillars, along with the faith of profession (Shahada), the five regular ritual prayers (Salat), charity (Zakat), and the pilgrimage to Mecca (Hajj). Muslims fast every day for a whole month during Ramadan (1).

Ramadan fasting involves abstaining not only from food and drink, but also from smoking, medication use, and sexual activity. Ramadan fasting is a unique form of fasting that consists of alternate cycles of abstinence and refeeding. Muslims start their fast by eating a pre-dawn meal called suhoor and end their fast by eating an after-sunset meal called iftar. It means that the mean fasting duration during abstinence periods is usually 12-14 hours per day. However, it also depends on the place and the time of the year (1).

Ramadan fasting is obligatory for every adult Muslim who has no medical or religious barriers. However, some groups are allowed not to fast in Ramadan, including travelers, children, women who are menstruating, pregnant, or breastfeeding, and anyone with an illness. In the Al-Quran, it is explained that if a person is sick and cannot fast according to the testimony of an expert and trusted doctor, he is allowed not to fast (1). Even so, sometimes the patient still wishes to fast. As a doctor in Indonesia, a country with a Muslim majority population, we will often get questions from patients, "Can I fast? and How does fasting affect my health?". This question will often be asked by patients, including patients with Chronic Kidney Disease (CKD) who are undergoing hemodialysis (2).

Chronic kidney disease is an incurable and chronic disease that is a significant public health concern in both developed and developing countries, where the prevalence of the disease continues to rise year after year (3).

CKD was described as kidney damage and/or a glomerular filtration rate (GFR) of 60 ml/men/1.73 m^2 for more than three months. CKD is classified into six stages based on the GFR value (4). CKD is also classified according to its severity, diagnosis, treatment, and prognosis (5). Renal function decreases in CKD as a result of progressive glomerular damage induced by maladaptive responses to functional cells in the kidneys to a variety of stresses, including inflammation, oxidative stress, and hypertension (6). CKD leads to irreversible retrograde of renal function that finally becoming an end-stage renal disease (ESRD). Hemodialysis (HD) is one of the therapies needed for patients with end-stage renal disease (ESRD). Indonesia is a country in South-East Asia, consisting of more than 13 600 islands and 400 ethnicities (7). In Indonesia, the

prevalence of HD patients increased from 9396 in 2013 to 11 689 in 2014, while the incident rate increased from 15 128 in 2013 to 17 193 in 2014 (8).

The primary issue that patients undergoing hemodialysis face is weight gain between two hemodialysis sessions, referred to as Interdialytic Weight Gain (IDWG). IDWG is an increase in fluid volume manifested by weight gain as a proxy for the amount of fluid ingested during the interdialytic cycle and the client's compliance with fluid control in hemodialysis patients (9). Fluid restriction is recommended for hemodialysis patients due to the inability of the kidneys to remove excess body fluids, and the risk of increased complications from the excess fluid as a fluid overload can lead to lower-extremity edema, ascites, and pulmonary vascular congestion, increased morbidity, and mortality in CKD patients (10).

Eventually, as Ramadan fasting imposes lifestyle changes in terms of meal timing, frequency, food availability, and food culture, it is reasonable to predict that dietary and fluid restriction can result in deterioration of nutritional and health status in patients with chronic kidney disease who practice fasting. Additionally, this study reported that Ramadan fasting results in a substantial decrease in IDWG (11). Based on a study (12), Ramadan fasting is beneficial for health in the general population. It can reduce the risk factor of atherosclerosis like reducing Trigliserid, body weight, and systolic blood pressure. However, Ramadan fasting does not affect cholesterol, fasting blood glucose, and diastolic blood pressure changes in general populations. Nevertheless, several studies mention that the impact of Ramadan fasting on CKD patients is still controversial. A study (2) found that Ramadan fasting in patients with CKD stage 3 or more can lead to a more progressive deterioration of kidney function. This is probably due to dehydration caused by limiting fluid and food intake during Ramadan fasting. In a healthy person, the body responds by secreting antidiuretic hormones that affect decreasing the production of urine and increasing urine concentration without any injurious effect on kidney function. However, in patients with different renal diseases, Ramadan fasting can affect body homeostasis and metabolism.

Yet, the safety study of Ramadan fasting in CKD patients on maintenance hemodialysis is still controversial. Commonly, patients with chronic kidney disease who receive hemodialysis are advised not to fast during Ramadan due to the increased risk of dehydration during the long fasting hours and the risk of fluid overload due to increased fluid intake after sunset (13). In other research, it was discovered that Ramadan fasting had no clinically significant effects on hemodialysis patients and was not associated with significant clinical complications. It is because spirituality plays a significant role in the lives of patients with chronic kidney disease, serving as a coping mechanism and contributing to the psychosocial adjustment to illness, thus allowing individuals to have a higher quality of life (13).

According to the definition above, publications examining the impact of Ramadan fasting on the health of hemodialysis patients remain scarce and contentious. There are no standards or guidelines in place. Additionally, knowledge available on the internet is often deceptive or inconsistent. In Indonesia, we have not found a similar study. So that further study is needed relating to this matter in Indonesia to answer these problems. This study aims to determine the effect of Ramadan fasting on clinical and laboratory parameters in CKD patients undergoing hemodialysis.

METHODS

This study was an analytical observational study with a cohort design conducted from April 1st to May 27th, 2020. It was held in the hemodialysis unit of Roemani Muhammadiyah Hospital Semarang, Indonesia. The sampling technique used in this study was consecutive sampling. The inclusion criteria were patients who underwent hemodialysis ≥ 3 months, frequency of hemodialysis twice a week, and willing to participate in the study. Meanwhile, patients with incomplete data who underwent fasting 1-29 days, got a blood transfusion, underwent a change in therapy regimen, died, and moved to other hemodialysis units during the study period were excluded from this study. In this study, there was no intervention in determining patient decisions and abilities to fast during Ramadan.

The independent variable in this study was fasting status which was categorized into fasting (fasting 30 days) group and non-fasting group. In comparison, the dependent variable in this study was clinical parameters which include pre-dialysis weight, Inter Dialysis Weight Gain (IDWG), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and laboratory parameters which include hemoglobin (Hb) levels. Pre dialysis weight, IDWG, SBP, and DBP were recorded a month before and during Ramadan. IDWG is calculated by calculating the difference in body weight in kilograms between pre-dialysis weights minus post-dialysis weight in the previous hemodialysis period. SBP and DBP were checked before the patient underwent hemodialysis, where the patient was asked to rest for at least 10 minutes before, and the measurement was done in an upright sitting position on the patient's arm where Cimino was not available as hemodialysis access. We took the differences between at the beginning of Ramadan and once after Ramadan is over for the clinical parameters. While Hb was measured using a peripheral blood sample taken before hemodialysis and examined using the spectrophotometry method. The collected data then tested for normality test and analyzed bivariate using SPSS 18.0.

RESULTS

In this study, 109 respondents underwent hemodialysis in Roemani Muhammadiyah Hospital, Semarang, Indonesia. Of them, 16 respondents did not meet inclusion because 6 respondents underwent hemodialysis <2x a week, and 10 respondents underwent hemodialysis <3 months. Of 93 respondents who met inclusion, 60 respondents were excluded from the study because 9 respondents died, 5 respondents got a blood transfusion, 5 respondents had incomplete data, and 41 respondents were observed 1-29 days of Ramadan fasting. After going through inclusion and exclusion, there were 33 respondents whose data could be analyzed. The sample selection flow chart in this study is shown in Figure 1.

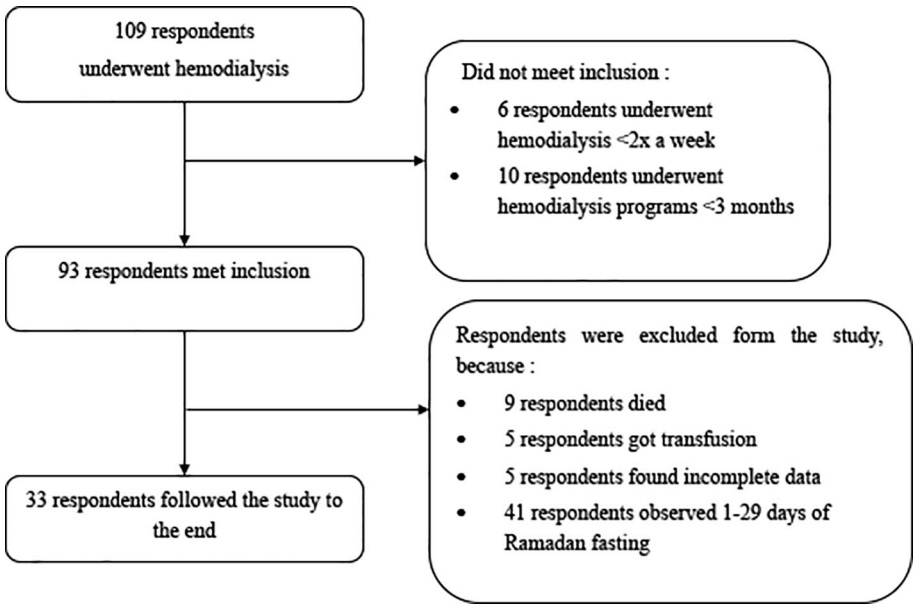

Figure 1. Sample selection flow Chart.

Of the 33 respondents, 11 (33.3 %) respondents were categorized into the fasting and 22 (66.7 %) respondents in the non-fasting group. Of them, 17 (51.5 %) respondents were male, and 16 (48.5 %) respondents were female. The mean age of respondents was 55.4 ± 10.5 years. The duration of hemodialysis was 24 ± 20.1 months. The mean eGFR was 6.2 ± 2 mL/min/1.73m^2. The mean urea and creatinine were 134.2 ± 30 mg/dL and 11.4 ± 2.9 U/L. The sociodemographic data are shown in Table 1.

Table 1

Sociodemographic Data

Variables	Mean ± SD
Age (years)	55.4 ± 10.5
Duration of hemodialisis (months)	24 ± 20.1
eGFR	6.2 ± 2
Ureum (mg/dL)	134.2 ± 30
Creatinine (mg/dL)	11.4 ± 2.9
Sex	
Male	17 (51.5%)
Female	16 (48.5%)

Descriptions data relate to the differences in pre-dialysis weight, IDWG, SBP, DBP, and Hb in the period before and during Ramadan are presented in Table 2. The normality test results using Shapiro-Wilk were carried out from all these data, and all data showed normal data (p>0.05). A statistical test was carried out using an independent t-test to see the effect of Ramadan fasting on clinical and laboratory parameters in CKD patients undergoing hemodialysis. From these data, it was found that there was a significant relationship between Ramadan fasting and pre-dialysis weight (p=0.003). On the other hand, we found no significant relationship between Ramadan fasting and other variables like IDWG, SBP, DBP, and Hb with p>0.05.

Table 2

Relationship of Ramadan fasting to clinical and laboratory parameters

Variable	Category	N	Mean ± SD	Mean difference	CI 95%	p-Value
Pre Dialysis Weight	Fasting	11	-0.5 ± 1.9	-0.3	-1.19 – 0.66	0.003
	Non fasting	22	-0.2 ± 0.7			
IDWG	Fasting	11	-0.3 ± 0.6	-0.2	-0.72 – 0.42	0.796
	Non fasting	22	-0.1 ± 0.8			
SBP	Fasting	11	-2.9 ± 10.6	-1.8	-8.3 – 4.7	0.632
	Non fasting	22	-1.1 ± 7.6			
DBP	Fasting	11	-0.8 ± 7.6	-0.7	-5.82 – 3.73	0.076
	Non fasting	22	-0.1 ± 4.8			
Hb	Fasting	11	0.2 ± 0.8	0.2	-0.44 – 0.84	0.726
	Non fasting	22	0 ± 0.8			

Note: N=Number of Respondents, SD=Standard Deviation, CI=Confident Interval, IDWG=Inter Dialytic Weight Gain, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, Hb=Hemoglobin

DISCUSSION

This study found a significant relationship between Ramadan fasting and pre-dialysis weight, and similar results have been obtained in the previous report (14). In contrast, other studies showed no association between Ramadan fasting and pre-dialysis weight (15,16). This may be due to differences in eating habits during Ramadan as well as varying levels of activity during Ramadan (14).

In this study, there was no significant relationship between Ramadan fasting and IDWG, similar to other studies (15,16). In this study, it was found that the IDWG decreased both in the fasting and non-fasting group. In contrast, a study (13) showed an increase in IDWG. It is suspected that this is closely related to the changes in the patient's daily fluid intake. However, in this study, no data were collected regarding fluid consumption before and during Ramadan (13).

In this study, there was no significant relationship between Ramadan fasting and SBP. This is similar to previous studies (15,16). However, a report showed a significant relationship between Ramadan fasting and SBP (17). The systolic period is a period of filling in the heart which followed by a period of contractions. Self-control, carried out by people who fast in Ramadan, can make us calm, can control ourselves, and not be reckless, so we do not get angry easily. This can prevent the release of the hormone adrenaline or epinephrine so that vasoconstriction does not occur and affects SBP. It is suspected that the vasodilation mechanism of blood vessels does not affect the SBP of respondents during Ramadan fasting (12).

In this study, it was found that there was no significant relationship between Ramadan fasting and DBP, which is similar to the previous study (15). In contrast, another reported study showed a significant relationship between Ramadan fasting and DBP (17,18). Diastolic is the phase when the heart relaxes. There is a decrease in oxidative stress during fasting so that Nitric Oxide (NO) function is not disturbed. One of the functions of NO is to cause vasodilation. It is suspected that the vascular vasodilation mechanism does not affect DBP in respondents during Ramadan fasting (12).

In this study, it was found that there was no significant relationship between Ramadan fasting and Hb level, in line with other reports (15,17). However, this finding was in contrast to recent studies, which showed a significant relationship between fasting Ramadan and Hb levels (19,20). There was a decrease in Hb levels in hemodialysis patients in the fasting and non-fasting groups, while there was an increase in Hb levels in both fasting and non-fasting group hemodialysis patients, although it was not statistically significant. This is probably because Ramadan is a special month for Muslims so that they will prepare a menu with better nutritional value during Ramadan (20).

CONCLUSION

In this study, it was found that there was a significant relationship between Ramadan fasting and pre-dialysis weight in CKD patients undergoing hemodialysis. However, on the other hand, Ramadan fasting does not relate to IDWG, SBP, DBP, and Hb level parameters in CKD patients undergoing hemodialysis. These results indicate that hemodialysis patients who are fasting are the same as those who are not fasting, so it is safe if hemodialysis patients wish to fast in Ramadan.

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ARTÍCULO ORIGINAL

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Effect of astaxanthin on malondialdehyde level in damaged cerebral cortex tissue in male rat (*Rattus Norvegicus*) induced by formaldehyde orally

Efecto de la astaxantina sobre el nivel de malondialdehído en el tejido de la corteza cerebral dañada en ratas macho (*Rattus norvegicus*) inducido por formaldehído por vía oral

Erik Ahmad Hasyim[1*•], Virhan Novianry[2*], Mistika Zakiah[3*], Andriani[4*], Dyan Roshinta Laksmi Dewi[5**]

SUMMARY

Background*: Malondialdehyde (MDA) is a dialdehyde substance that is the final product of lipids peroxidation in the human body, and it can be used as a biomarker of oxidative stress. One of the most potent antioxidants known nowadays is astaxanthin. This study aims to investigate the effect of astaxanthin on the MDA level in cerebral cortex tissue of Rattus norvegicus, which was given oral formaldehyde.*
Methods*: This study used 25 Wistar rat model (Rattus norvegicus) which were divided into five groups: negative control, normal control groups, astaxanthin 12 mg/day, 24 mg/day, and 48 mg/day groups.*
Results*: The mean tissue MDA levels in normal control group was 11.10 ± 5.11 nmol/mL, negative control group was 9.74 ± 5.19 nmol/mL, astaxanthin 12 mg/day group was 10.71 ± 4.92 nmol/mL, 24 mg/day group was 13.14 ± 3.34 nmol/mL, and 48 mg/day groups was 6.10 ± 1.83 nmol/mL. Compared with the normal control group and negative control group, there was no significant difference (p>0.05), respectively, with the treatment-3 group of astaxanthin.*
Conclusion: *There were not effective doses of astaxanthin (12 mg/day, 24 mg/day, and 48 mg/day) in this study that significantly reduced MDA levels in cerebral cortex tissue, in oral formaldehyde induced male Rattus norvegicus.*

Keywords*: Antioxidant, astaxanthin, cerebral cortex, formaldehyde, malondialdehyde, oxidative stress.*

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RESUMEN

Antecedentes: *El malondialdehído (MDA) es una sustancia dialdehído que es el producto final de la peroxidación de los lípidos en el cuerpo humano y se puede utilizar como biomarcador de estrés oxidativo. Uno de los antioxidantes más potentes que se conocen hoy en día es la astaxantina. Este estudio tiene como objetivo investigar el efecto de la astaxantina en el nivel de MDA en el tejido de la corteza cerebral de Rattus norvegicus, al que se le administró formaldehído oral.*
Métodos: *Este estudio utilizó 25 modelos de ratas Wistar (Rattus norvegicus) que se dividieron en cinco grupos: control negativo, grupos de control normal, grupos de astaxantina 12 mg/día, 24 mg / día y 48 mg / día.*
Resultados: *Los niveles medios de MDA en tejido en el grupo de control normal fue de 11,10 ± 5,11 nmol/ mL, el grupo de control negativo fue de 9,74 ± 5,19 nmol / mL, el grupo de astaxantina 12 mg / día fue de 10,71 ± 4,92 nmol / mL, el grupo de 24 mg / día fue 13,14 ± 3,34 nmol / mL, y los grupos de 48 mg / día fueron 6,10 ± 1,83 nmol / mL. En comparación con el grupo de control normal y el grupo de control negativo, hubo una diferencia insignificante (p> 0.05), respectivamente, con el grupo de tratamiento-3 de astaxantina.*
Conclusión: *No hubo dosis efectivas de astaxantina (12 mg / día, 24 mg / día y 48 mg / día) en este estudio que redujeran significativamente los niveles de MDA en el tejido de la corteza cerebral, en Rattus norvegicus macho inducido por formaldehído oral.*

Palabras clave: *Antioxidante, astaxantina, corteza cerebral, formaldehído, malondialdehído, estrés oxidativo.*

INTRODUCTION

The cerebral cortex is the neural tissue in cerebral hemispheres containing mostly grey matter. Memory, attention, perceptual awareness, mental language, and consciousness are all facilitated by the cerebral cortex. The cerebral cortex of adult mammals comprises six layers with nerve cell bodies, dendritic arborizations, and synaptic interconnections (1). In humans, the cerebral cortex consists of approximately 80 % of the whole brain mass. It is estimated that there are 10 to 16 billion neurons in the cortex of the adult human brain with an estimated average mass of 1 233 g, and the number of neurons above is only an estimate, meaning that the number can be less or more (2). The cerebral cortex has a variety of roles in maintaining the essential functions of life. This does not make the cerebral cortex invulnerable to various metabolic, toxic, microbial, and circulatory disorders. Various diseases related to damage or disorders in the cerebral cortex are among the highest in Indonesia (3). Indonesia is the fourth most populous country in the world, located in Southeast Asia, with a total population of ~260 million in 2017, which is composed of various ethnic groups (4). Based on data from the Indonesian Hospital Association in 2009, diseases related to damage of the cerebral cortex area cause up to 65 % of disabilities (3).

Formaldehyde is a molecule that degrades rapidly in the environment and the human body has been related to neurodegenerative disease. Neurodegenerative disease is a disorder of the nervous system which may result in neuron degeneration or atrophy (5-7). Cerebral cortex tissue damage caused by free radicals can derive from formaldehyde metabolism (8,9). A free radical is an atom with an unpaired electron that becomes unstable and reactive as a result. Free radicals could harm the body's critical macromolecules resulting in cell damage and disruption of homeostasis (10). Based on a study (11), formaldehyde exposure can cause oxidative stress by increasing the production of Reactive Oxygen Species (ROS) compounds in the body (11). Oxidative stress can lead to degenerative diseases. According to the World Health Organization (WHO), approximately 17 million people die each year from degenerative disease (10). This oxidative damage often causes severe problems in susceptible neurons such as the frontal cortex, entorhinal cortex, and the substantia nigra in general, which are the most significant constituents of the cerebral cortex, causing cell damage, death, and leading to neurodegenerative processes, such as Alzheimer's disease, Parkinson's disease, and lateral amyotrophic sclerosis (12).

Malondialdehyde (MDA) is a dialdehyde molecule that is formed by free radicals during ionization events in the body (13). The quantity of malondialdehyde (MDA) in the blood may indicate oxidative stress levels in the organism. MDA levels in the blood increase in correlation with the body's oxidative stress (14).

Antioxidants are necessary chemicals compound for the body to neutralize free radicals and prevent free radicals' damage. Antioxidants stabilize free radicals by compensating for the electron deficiency of free radicals and preventing chain events caused by free radical generation that might result in oxidative stress (15). The human body is producing endogenous antioxidants, such as superoxide dismutase (SOD). The huge amount of ROS produced by body cells creates an imbalance condition. This imbalance could reduce the level of endogenous antioxidants. So, it is important to increase the number of exogenous antioxidants to avoid the harmful effects of free radicals (16). One of the antioxidants that are known to have a reasonably strong effect is astaxanthin (17,18). Astaxanthin, produced from *Haematococcus pluvalis*, is the most powerful and safest carotenoid without pro-oxidant effects, comparable to beta-carotene, lycopene, zeaxanthin, and lutein. It has three critical triple properties: antioxidant, anti-inflammatory, and immunomodulator. Astaxanthin reduces the production of inflammatory genes by inhibiting NF-kB activation and protects cells from oxidative damage, therefore astaxanthin also has anti neurodegenerative properties (19). A study conducted by Tso and Lam (1996) showed that compared to beta-carotene, astaxanthin was easier to cross the blood-brain barrier so that it can function as a good antioxidant for the brain (20).

The objective of this study was to examine the effect of astaxanthin on the MDA level in the cerebral cortex tissue of Wistar strain *Rattus norvegicus* that had been exposed to oral formaldehyde and to identify the optimal dose of astaxanthin as an antioxidant based on the MDA level in the damaged cerebral cortex tissue.

METHODS

Materials to be used in this research are stored biological materials, astaxanthin, formaldehyde 37 %, distilled water, standard food, wood powder, phosphate-buffered saline (PBS) 0.1 M Ph 7.4, thiobarbituric acid (TBA) 0.67 %, tetra ethoxy propane (TEP), and trichloroacetic acid (TCA) 20 %. The tools used in this research were rat cage, oral syringe, gastric syringe, spectrophotometer, centrifuge, analytical scale, animal scale, TissueLyser II (QIAGEN), blender, micropipette, 1 000 mL measuring cup, 100 mL measuring cup, 10 mL measuring flask, shaker, test tube, handscoon, microtube, vortex, UV-sterile, hot plate, iron stirrer, and PH-meter.

The sample was taken by simple random sampling technique, sampling is done by selecting available members of the population, randomly. In this study, the sample was obtained from *Rattus norvegicus* Wistar strains with several criteria: three months old, 200-gram rat body weight, and good general health. The sample size was 25 white rats, which were divided into five groups randomly.

Then tested animals were divided into five groups, with five rats in each group. The negative control group was given formaldehyde 0.01 mL; the normal control group was given distilled water and standard diet; treatment-1, treatment-2, and treatment-3 groups were given astaxanthin 12 mg/day, 24 mg/day, and 48 mg/day, respectively, for 14 days after being given formaldehyde for 14 days.

Measurement of MDA levels was carried out by measuring the absorbance of each experimental group. The measurement method used was the TBA method. TBA has a high sensitivity value to free radicals. TBA will react with carboxylate groups from MDA through the addition of nucleophilic to form a TBA-MDA complex in an acidic atmosphere and form a pink color so that it can be quantified by spectrophotometry. The results of the data obtained were processed with IBM SPSS Statistics v22.0 for Windows. The data were tested using the One-Way ANOVA hypothesis test followed by the Post Hoc LSD test.

RESULTS

Standard curve determination was carried out before measuring the MDA level of the sample tissue. From the determination of this standard curve, the sample wavelength and the standard curve equation will be obtained and be used to calculate the MDA level of the sample. The standard curve used is TEP. TEP, when reacted with TBA, will form MDA and methanol as byproducts. Measurements were made at six standard TEP concentration points

with a concentration of 0.15625 nmol/mL, 0.3125 nmol/mL, 0.625 nmol/mL, 1.25 nmol/mL, 2.5 nmol/mL, and 5 nmol/mL. The standard curve equation obtained is:

$Y = 0.058\ X + 0.010$

With $a = 0.058$

$b = 0.010$

Relation coefficient (r) = 0.999

From this formula, the linear regression curve between the MDA standard solutions on the absorbance can be seen in Figure 1.

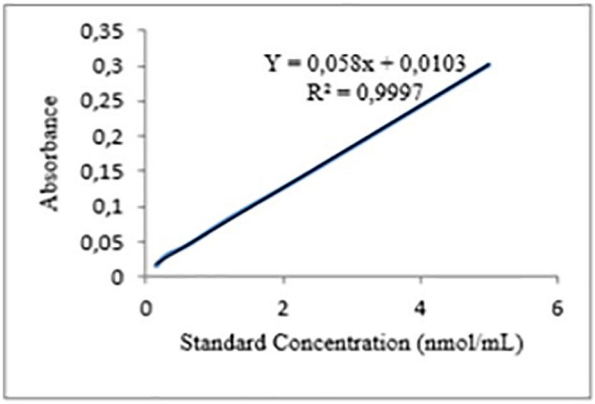

Figure 1. Linear regression curve of the MDA standard.

All absorbance obtained in the treatment group was calculated using the formula for MDA levels, comparing the absorbance with a standard curve, using the standard curve equation as follows:

MDA level = $df \times (x$ / sample volume)

With df = diluting factor

The mean tissue MDA levels are shown in Table 1. The MDA levels of the cerebral cortex were statistically analyzed using the One-Way ANOVA test and the Post Hoc test. MDA levels from the five groups were analyzed using the One-Way ANOVA test. The differences in MDA levels between each group were analyzed using the Post Hoc test.

Table 1

Comparison of MDA Level between Groups

Tested Groups	Mean ± SD MDA Levels (nmol/mL)
Normal control group	11.10 ± 5.11
Negative control group (K-)	9.74 ± 5.19
Treatment-1 group (K1)	10.71 ± 4.92
Treatment-2 group (K2)	13.14 ± 3.34
Treatment-3 group (K3)	6.10 ± 1.83

Note. K1=astaxanthin dosage of 12 mg/day, K2=astaxanthin dosage of 24 mg/day, K3=astaxanthin dosage of 48 mg/day.

A comparison diagram of MDA levels in the cerebral cortex tissue of each treatment group can be seen in Figure 2.

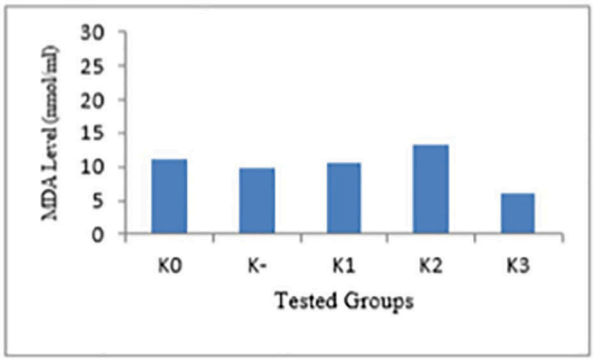

Figure 2. Mean MDA levels in cerebral cortex tissue.

DISCUSSION

The Post Hoc test results showed the results of the comparative analysis of MDA levels between each treatment group. Measurement of MDA levels in the normal group is used compared to the treatment groups. Normal group had insignificant different levels of MDA, compared to the negative group. The negative control group was the only group that given oral formaldehyde exposure without given astaxanthin. MDA

levels in the normal group were higher than in the negative control group, this difference was not significant in statistical tests. This is because the formaldehyde levels that reach the cerebral cortex are less than the initial exposure dose of 0.01 mL/day, thus showing the result was found. Formaldehyde can combine with cellular constituents easily in all exposed tissues throughout its route. This process occurs mainly in the liver and to a lesser extent in erythrocytes, kidneys, muscles, and the brain. This is also supported by the evidence that the half-life of formaldehyde so that it is converted to formic acid is very fast, which is about 1.5 minutes (21).

The following comparison is between the normal group and the treatment groups. The treatment groups were given oral formaldehyde and astaxanthin exposure. There were three different doses used, that was 12 mg/day (K1), 24 mg/day (K2), and 48 mg/day (K3). Although the 12 mg/day and 48 mg/day dose groups had different levels of MDA compared to normal control group, this cannot yet be said to be an effect of astaxanthin in that group. These conclusions were drawn for two reasons. The first is that the statistical test showed that the difference was not significant, and the second is that MDA levels in the negative control group were also relatively insignificant lower than the normal control group. This is because the astaxanthin doses of 12 mg/day and 24 mg/day have not significantly inhibited lipid peroxidation in the cerebral cortex tissue after exposure to formaldehyde in these two groups. The third treatment group was analyzed, only the 48 mg/day dose group had lower MDA levels than the negative control group, although the Post Hoc test showed that this difference was not significant.

Among the numerous natural carotenoids, astaxanthin is regarded as one of the most effective at protecting membrane cells, lipids, and lipoproteins from oxidative damage (22). The polyene chain in the chemical structure of astaxanthin can trap free radicals in the cell membrane while the terminal ring tames free radicals on the inner and outer sides of the cell membrane, promote the preservation of cell membrane structure thus inhibiting lipid peroxidation, which leads to increased MDA level (23).

The analysis of MDA levels obtained from the three doses of astaxanthin showed that the most effective dose was 48 mg/day if compared with the two other doses. The dose of 48 mg/day reduced MDA levels so that it was not significantly different from the negative control group and the normal control group.

CONCLUSION

These results indicate no effective dose of 12 mg, 24 mg, and 48 mg of astaxanthin which significantly reduced the MDA levels of the cerebral cortex tissue in the male *Rattus norvegicus* Wistar strain that was induced by formaldehyde orally. Future studies are needed to assess the therapeutic effect of astaxanthin by looking at the histopathological features of the cerebral cortex.

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Intradialytic and post-dialytic complications in chronic kidney disease patients undergoing maintenance hemodialysis

Complicaciones intradialíticas y posdiálisis en pacientes con enfermedad renal crónica sometidos a hemodiálisis de mantenimiento

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SUMMARY

Background: *Acute complications can happen during dialysis or after dialysis, and often those complications are inevitable. Although hemodialysis is claimed to be a relatively safe option, these complications often bring significant discomfort for chronic kidney disease (CKD) patients. This study was to determine CKD patients' characteristics and figure out the frequencies and varieties of acute hemodialysis complications.*
Methods: *A descriptive cross-sectional study was conducted from July 01, 2020, to August 01, 2020, at the dialysis unit of Arsani hospital, Indonesia. The data for this study were taken using history taking and monitoring the patients during the dialysis process.*
Results: *A total of 25 patients met the criteria and were observed in one month study period. There were 14 (56 %) males and 11 (44 %) females. The most common etiology of CKD was hypertension (68 %), followed by type 2 diabetes (24 %), and nephrotic syndrome (8 %). Among 251 hemodialysis sessions, 85 (33.8 %) of them experience one or more intradialytic or post-dialytic complications. Acute hypertension (18.7 %) and fatigue (18.7 %) were both the most common complications, followed by gastrointestinal manifestations (17.1 %), fever (13.0 %), acute hypotension (11.4 %), muscle cramps (7.3 %), hypoglycemia (1.6 %), and others (12.2 %).*
Conclusion: *Acute complications in hemodialysis are prevalent, and most are not life-threatening. Monitoring, rapid treatment, and good nutritional status are necessary to overcome those complications and maintain CKD patients' quality of life.*

Keywords: *Chronic kidney disease, hemodialysis, intra- & post-dialytic complication.*

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RESUMEN

Antecedentes: *Las complicaciones agudas pueden ocurrir durante la diálisis o después de la diálisis y, a menudo, esas complicaciones son inevitables. Aunque se afirma que la hemodiálisis es una opción relativamente segura, estas complicaciones a menudo provocan un malestar significativo para los pacientes con enfermedad renal crónica (ERC). Este estudio fue para determinar las características de los pacientes con ERC y averiguar las frecuencias y variedades de complicaciones agudas de la hemodiálisis.*

Métodos: *Se realizó un estudio descriptivo transversal desde el 01 de julio de 2020 al 01 de agosto de 2020, en la unidad de diálisis del hospital Arsani, Indonesia. Los datos para este estudio se tomaron utilizando la historia clínica y el seguimiento de los pacientes durante el proceso de diálisis.*

Resultados: *Un total de 25 pacientes cumplieron los criterios y fueron observados en un período de estudio de un mes. Había 14 (56 %) hombres y 11 (44 %) mujeres. La etiología más común de la ERC fue la hipertensión (68 %), seguida de la diabetes tipo 2 (24 %) y el síndrome nefrótico (8 %). Entre las 251 sesiones de hemodiálisis, 85 (33,8 %) de ellas experimentan una o más complicaciones intradiálisis o posdiálisis. La hipertensión aguda (18,7 %) y la fatiga (18,7 %) fueron las complicaciones más frecuentes, seguidas de las manifestaciones gastrointestinales (17,1 %), fiebre (13,0 %), hipotensión aguda (11,4 %), calambres musculares (7,3 %), hipoglucemia (1,6 %) y otros (12,2 %).*

Conclusión: *Las complicaciones agudas en hemodiálisis son prevalentes y la mayoría no ponen en peligro la vida. La monitorización, el tratamiento rápido y un buen estado nutricional son necesarios para superar esas complicaciones y mantener la calidad de vida de los pacientes con ERC.*

Palabras clave: *Enfermedad renal crónica, Hemodiálisis, complicación intra y posdiálisis.*

INTRODUCTION

The number of chronic kidney disease (CKD) patients is increasing each year and is predicted to be constantly abundant in the future. There are five stages of CKD with End-Stage Renal Disease (ERDS) as its end-stage (1). ESRD has become the primary concern in the medical world due to its high prevalence, increasing cardiovascular risk, and mortality rate (2). The prevalence of chronic kidney disease is increasing around the world. According to Basic Health Research, the prevalence of CKD in Indonesia is about 0.2 % in 2013 to 0.38 % in 2018 (3-5). CKD is defined as irreversible loss of renal function to excrete metabolite waste products and regulate fluid homeostasis, which means patients with ERDS need to undergo renal replacement therapy (RRT), including renal transplantation, peritoneal dialysis, or hemodialysis. Besides pharmacological treatment, hemodialysis is one of the most common therapy for CKD patients (6). Hemodialysis is a process of removing the waste metabolic product and toxic substances out of the body. While the hemodialysis process is happening, metabolic and hemodynamic changes will occur. These changes will bring several complications in a short or long period (7). This effect can be felt by the patient while having the dialysis or after the dialysis process, which can influence the quality of life of CKD patients (6,8).

Usually, CKD patients undergoing hemodialysis treatment spend 9-12 hours a week in a dialysis unit. Each session lasts for about 3-5 hours, and it is performed 2-3 times a week (8). Although it is recommended to do hemodialysis three times a week, many practitioners still scheduled their patients for twice a week hemodialysis, mainly in developing countries in Asia or Africa (9). Generally, the frequency of hemodialysis in Arsani Hospital, Bangka Belitung, Indonesia, is twice a week. Usually, three-time-session hemodialysis is scheduled for patients who experience worse signs and symptoms of the disease.

Hemodialysis is claimed to be relatively safe, but actually, it often comes with several acute complications. Acute complications are defined as signs or symptoms within the dialysis or 24 hours after the dialysis session. It varies from hypotension, hypertension, shivering, gastric problem, muscle soreness, fatigue, and many more (1). Sometimes, a hemodialysis session is stopped because of unbearable complications. Those complications can cause issues that are even more complicated such as stress, low quality of life, or even death (8,10).

This study aims to determine the characteristics of CKD patients in Arsani hospital Indonesia; to find out the prevalence of acute intradialytic and post-dialytic complications of patients with

ESRD that undergo hemodialysis. The purpose of this study also to see if hemodialysis is a relatively safe option for CKD patients. This study is hoped to be a reference for healthcare to anticipate and manage the upcoming complications.

METHODS

This study was a descriptive study with a cross-sectional design. The data were collected from 1st July 2020 to 1st August 2020 in the hemodialysis unit of Arsani Hospital, Sungailiat, Bangka Belitung, Indonesia. The dialysis unit in Arsani Hospital had eight beds for patients without infectious diseases and one bed for patients with infectious diseases, such as Hepatitis type B and C. The population of this study was CKD patients that came to the dialysis unit to do regular hemodialysis. Samples were chosen by using non-probability sampling, which was quota sampling. The total of samples were 25 patients, including men and women.

The samples for this study met the inclusion and exclusion criteria. Inclusion criteria were patients already done the hemodialysis session for at least 3 months and routinely doing 2 -3 sessions each week. Exclusion criteria were patients with acute kidney injury that only needed emergency hemodialysis, patients with congenital kidney disease such as kidney agenesis, kidney artery stenosis, or polycystic kidney disease (11).

Intradialytic hypertension was defined as increasing mean arterial pressure (MAP) ≥15 mmHg during or after hemodialysis. Meanwhile, intradialytic hypotension meant decreased systolic blood pressure ≥20 mmHg or systolic blood pressure was observed to be <90 mmHg during or after the hemodialysis session (12). Other acute complications such as nausea, vomiting, epigastric discomfort, headache, fatigue, muscle soreness, muscle cramps were observed intra-dialysis or post-dialysis. Blood glucose measurement was tested while necessary.

RESULTS

A number of 25 patients undergoing routine hemodialysis were observed for one month starting July 2020 until August 2020. Among those patients, 14 were male (56 %), and 11 were female (44 %). Based on Table 1, most of the samples have normal body mass index (40 %), followed by obese (28 %) and overweight (24 %).

Table 1

Basic characteristics of the subjects

Category	Frequency (%)
Sex	
Male	14 (56.0)
Female	11 (44.0)
Age	
<40 years old	4 (16.0)
40 – 49 years old	5 (20.0)
50 – 59 years old	5 (20.0)
≥60 years old	11 (44.0)
Body mass index	
Underweight	2 (8.0)
Normal weight	10 (40.0)
Overweight	6 (24.0)
Obese	7 (28.0)

These patients were diagnosed with CKD with various etiologies; the most common etiology was hypertension (68 %). Other etiologies were type 2 diabetes (24 %), nephrotic syndrome (8 %). Among all patients, 18 (72 %) patients undergo hemodialysis sessions twice a week, and 7 (28 %) patients have three times a week session.

Table 2 describes the acute complications during or after hemodialysis. There were 123 acute complications found in the observation of this study. Some patients even experienced more than one complication during the hemodialysis process. Hypertension and fatigue (18.7 %) were the most common acute complications to be found, followed by gastrointestinal manifestations such as nausea, vomiting, or epigastric pain (17.1 %).

There was a significant association between body mass index (BMI) and acute complication during or after dialysis in CKD patients (p-value= 0.043), as seen in Table 3.

Table 2

Distribution of acute intradialytic and post-dialytic complications

Acute complications	Frequency (%)
Hypertension	23 (18.7)
Hypotension	14 (11.4)
Fever	16 (13.0)
Gastrointestinal manifestation	21 (17.1)
Muscle cramps	9 (7.3)
Hypoglycemia	2 (1.6)
Fatigue	23 (18.7)
Others	15 (12.2)
Total	123 (100.0)

Table 3

Correlation between body mass index and acute intradialytic and post-dialytic complications

BMI	Acute complications							p-value
	Hypertension/ hypotension	Fever	GI manifestations	Muscle manifestation	Hypoglycemia	Others	Total	
UW	1 (11.1 %)	0 (0.0 %)	3 (33.3 %)	3 (33.3 %)	1 (11.1 %)	1 (11.2 %)	9 (100.0 %)	0.043
NW	14 (29.8 %)	3 (6.3 %)	12 (25.6 %)	11 (23.4 %)	0 (0.0 %)	7 (14.9 %)	47 (100.0 %)	
OB	22 (32.8 %)	13 (19.4 %)	6 (8.9 %)	18 (26.9 %)	1 (1.5 %)	7 (10.5 %)	67 (100.0 %)	
Total	37 (30.1 %)	16 (13.0 %)	21 (17.1 %)	32 (26.0 %)	2 (1.6 %)	15 (12.2 %)	123 (100.0 %)	

Note: BMI=body mass index, UW=underweight, NW=normal weight, OB=overweight-obese, GI=gastrointestinal.

DISCUSSION

Among all 251 hemodialysis sessions observed in this study, 85 patients (33.8 %) were involved in at least one acute complication. This result is per the previous study. This result is relatively high, but the percentage of acute complications follows a study in Eritrea, Eastern Africa, that found out the percentage of acute complications found in 30.7 % of all hemodialysis sessions (11). Hypertension and fatigue are the most common complications, followed by gastrointestinal manifestation, fever, hypotension, muscle cramps, and hypoglycemia. Other complications include headache, itching, and sensation of spinning.

Acute hypertension was defined as increased MAP ≥ 15 mmHg during or 24 hours after the dialysis session. Meanwhile, acute hypotension meant decreased systolic blood pressure ≥ 20 mmHg or systolic blood pressure was lower than 90 mmHg (12). In this study, hypertension was one of the most common complications and was higher than the previous study, with the percentage of acute hypertension only 5.06 % (11). The difference could happen because the total samples with hypertension as the main disease etiology were way higher in this study. Patients with ERDS lose the function to filter waste products and maintain homeostasis.

Hemodialysis could help to remove waste products, such as urea, creatinine, and many more. However, during the hemodialysis process, there was a significant change in plasma volume, and it can cause hemodynamic instability. Ultrafiltration, cardiac factors such as left ventricular hypertrophy could be the reason for

intradialytic complications (13). Administration of oxygen, placing the patient in Trendelenburg position, or discontinuing hemodialysis can be options to treat acute hypotension in hemodialysis and preventing life-threatening conditions (6).

In this study, fever was found in 13 % among all sessions. The temperature of dialysate could affect body temperature. Normal human body temperature varies from 36.5 ºC-37.5 ºC. Dialysate temperature of more than 37.5 ºC can cause fever that manifests as shivering in patients. Room temperature also held key factor in causing fever in patients. To prevent fever from happening, maintaining dialysate temperature, the room temperature was crucial (14).

Gastrointestinal manifestations were commonly found in this study, and it was higher than previous studies in Labore, Pakistan (9 %) and Surabaya, Indonesia (7.69 %) (11,14,15). Gastric manifestations vary from gastric pain, nausea, or even vomiting. Uremia also contributes to gastrointestinal manifestations, patients having only twice a week-dialysis sessions had a bigger risk to have high blood urea levels. Gastrointestinal manifestations could happen because of changes in blood pressure, anxiety, eat less or overeat during the session. In this study, the patients felt gastrointestinal manifestations mostly because they overate during the session. Patients who felt this complication were given antihistamine injection (Ranitidine 50 mg/2 mL) (14).

Muscle cramps could happen because of plasma volume depletion, imbalance of electrolytes, or high ultrafiltration rate. Patients with CKD lose their ability to balance certain electrolytes such as potassium and calcium. Dialysis did help the kidney to remove some electrolytes. However, this sudden change could cause patients to feel muscle cramps. In this study, muscle cramp was found in 7.3 % of all sessions, usually, the patients were recommended to do stretching before and after dialysis to cope with the muscle soreness (14).

Hypoglycemia rarely happened in this study. The number similar to the recent study, which was 1.8 %, was low glucose level (≤ 60 mg/dL) (16). Hypoglycemia during or after hemodialysis was less found because in Arsani hospital Indonesia, blood sugar levels were only tested if patients had the signs of hypoglycemia such as sweating, pallor, or loss of consciousness (1). Intradialytic hypoglycemia often happened to patients with type 2 diabetes that were prescribed insulin. Prescribing oral anti-diabetic causes less risk of hypoglycemic episodes in a hemodialysis patient.

Fatigue in CKD patients was often found in this study. Routine hemodialysis takes 3-5 hours for each session, and often patients could feel tired physically and mentally (11). However, sometimes fatigue is also correlated to patients' medical conditions, such as anemia, uremia, malnutrition, and many other conditions. Some patients could feel fatigued because of being immobile for several hours. It is recommended to do aerobic exercise daily and also simple exercise during dialysis to reduce muscle soreness and reduce depression (17).

Other complications include headache, the sensation of itch, and the sensation of spinning. Headache mostly happened because of metabolic changes during the hemodialysis process; sometimes, acute hypertension or hypotension could also cause headaches. Itching is often found in the patient with high blood urea level. Hemodynamic instability (sudden hypertension or sudden hypotension) and low hemoglobin level could be the cause of lightheadedness, the spinning sensation (1).

Most of the patients in this study were overweight or obese, followed by normal weight and underweight. Although BMI measurement cannot differentiate fat mass and lean mass, some studies showed that BMI was a predisposing factor for intradialytic hypotension in hemodialysis sessions (18). Poor nutritional status (low BMI) was associated with higher mortality in CKD patients (19). A study stated that CKD patients with high BMI (except > 40 kg/m2) had a lower mortality rate than CKD patients with lower BMI (< 18.5 kg/m2) (20). There was a significant association between BMI and acute complications in hemodialysis, with underweight and overweight patients being more prone to experiencing acute dialysis complications in this study.

This study provided important information, especially for healthcare in Arsani Hospital and other hospitals around the city. The limitation of this study was the limitation of samples and the short duration of observation. Lack of laboratory checking such as blood glucose level

and kidney function test for the patients due to limited resources.

CONCLUSION

The number of acute complications during dialysis and post-dialysis is high. Acute complications during and after hemodialysis are commonly not preventable. However, those complications can be anticipated and treated rapidly. Healthcare that works in the hemodialysis unit is recommended to have essential skills and awareness in coping with those complications.

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Pulmonary tuberculosis patients with diabetes mellitus have a more severe degree of chest X-ray compared to pulmonary tuberculosis patients without diabetes mellitus

Los pacientes con tuberculosis pulmonar con diabetes mellitus tienen un grado más severo de radiografía de tórax en comparación con los pacientes con tuberculosis pulmonar sin diabetes mellitus

Muhammad Ramzi[1*], Muslim Andala Putra[2*•], Mohammad Subkhan[3*]

SUMMARY

Introduction: *Pulmonary tuberculosis (TB) cases increase along with the increase in diabetes mellitus (DM) cases. The purpose of this study is to compare the description of Thorax X-ray severity between pulmonary TB patients without DM and pulmonary TB patients with DM.*
Methods: *The design of this study was cross-sectional. Observations were made with medical record data and X-Ray Thorax results which three different radiology specialists then classified. Classification of X-Ray Thoracic Lung TB is divided into 3, including minimal lesions, medium lesions, and extensive lesions.*
Results: *The results showed that TB patients without DM had a thorax X-Ray severity degree of at least 9 patients (30.0 %), moderate as many as 12 patients (40.0 %), and an area of 9 patients (30.0). Whereas in TB patients with DM who had a thorax X-Ray severity degree of at least 3 patients (10.0 %), moderate as many as 9 patients (30.0 %), and an area of 18 patients (60.0 %). There was a significant difference in the chest X-ray severity between TB patients without DM and with DM (p=0.040).*
Conclusion: *Patients with pulmonary TB and DM have a more severe chest X-ray than patients with pulmonary TB who do not have DM.*

Keywords: *Thoracic x-ray classification, pulmonary tuberculosis, diabetes mellitus.*

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RESUMEN

Introducción: *Los casos de tuberculosis pulmonar (TB) aumentan junto con el aumento de casos de diabetes mellitus (DM). El propósito de este estudio es comparar la descripción de la gravedad de la radiografía de tórax entre pacientes con TB pulmonar sin DM y pacientes con TB pulmonar con DM.*
Métodos: *El diseño de este estudio fue transversal. Las observaciones se realizaron con los datos de la historia*

clínica y los resultados de los rayos X de tórax que luego clasificaron tres especialistas en radiología diferentes. La clasificación de la tuberculosis pulmonar torácica por rayos X se divide en 3, que incluyen lesiones mínimas, lesiones medianas y lesiones extensas.
Resultados: *Los resultados mostraron que los pacientes con tuberculosis sin DM tenían un grado de gravedad de la radiografía de tórax, de al menos 9 pacientes (30,0 %), moderado hasta 12 pacientes (40,0 %) y un área de 9 pacientes (30,0). Mientras que en los pacientes con TB con DM que tenían un grado de gravedad de la radiografía de tórax de al menos 3 pacientes (10,0 %), moderada hasta 9 pacientes (30,0 %) y un área de 18 pacientes (60,0 %). Hubo diferencia significativa en la gravedad de la radiografía de tórax entre los pacientes con tuberculosis sin DM y con DM (p= 0,040).*
Conclusión: *Los pacientes con TB pulmonar y DM tienen una radiografía de tórax más grave que los pacientes con TB pulmonar que no tienen DM.*

Palabras clave: *Clasificación radiográfica de tórax, tuberculosis pulmonar, diabetes mellitus.*

INTRODUCTION

Pulmonary tuberculosis (TB) is a respiratory infection caused by the bacteria *Mycobacterium tuberculosis* (1). *M. tuberculosis* is divided into ancient and modern bloodlines (2). M. tuberculosis bacteria have aerobic, gram-positive, non-motile properties and are acid-resistant bacteria. Diseases caused by these bacteria are often found in densely populated environments because these bacteria are easy to breed in humid places. Symptoms caused by the *M. tuberculosis* bacteria include a prolonged cough which is sometimes accompanied by blood, fever, night sweats, drastic weight loss, and often feeling tired (3). TB has an impact not only on their physique but also on their quality of life (4).

Pulmonary TB in Indonesia ranks 3rd in the world by contributing 8 % of all TB cases in the world so that pulmonary TB disease is the leading health problem faced by Indonesia (5). New cases of pulmonary TB in Indonesia reached 420,994 cases in 2018 (6). In Sidoarjo, Indonesia, there are quite a lot of pulmonary TB sufferers. Based on data recapitulated by the Sidoarjo Health Office, in 2017, there were 890 new TB BTA (+) cases, while the total number of TB cases was 2092 (7). Indonesia through the national pulmonary TB prevention program targets to eliminate TB in 2035 and free from pulmonary TB in 2050 (8). However, there are still many problems found in preventing TB including lack of knowledge regarding TB (9) and resistance to the drug such as rifabutin (10).

The prevalence rate of TB increases along with the increase in cases of diabetes mellitus (DM). A study reported that new TB patients were found more in patients suffering from DM compared to patients who did not have a history of DM in Indonesia around 2001-2005 (11) DM causes the patient's immunity to becoming weak so that it can cause serious complications, one of which is susceptibility to infection, including by *M. Tuberculosis* (12) Additionally, a previous study found that the majority of patients with pulmonary TB who had type 2 diabetes have average high blood glucose and uncontrolled diabetes (13). In addition, DM may influence the success of pulmonary TB treatment (14).

Diagnosis in pulmonary TB patients can be made with a sputum smear test, plain X-ray Thorax, and most recently, it can be done with a molecular rapid test (15). The radiological results of pulmonary TB patients without DM and pulmonary TB with DM can be distinguished. In pulmonary TB with DM, atypical lesions are found, the infiltrates are abundant in the lower lobe then followed in the middle, some patients are found in the upper lobe, and pleural effusions can be found. Meanwhile, it is inversely proportional to pulmonary TB without DM. The infiltrates tend to be more found in the upper part of the lung (16). Previous studies concluded that there was no relationship between pulmonary TB patients with DM and without DM based on the Thorax photo image at PKU Muhammadiyah Yogyakarta Hospital, Indonesia (11). Based on the aforementioned research, this study seeks to establish a difference in the severity of the X-Ray Thorax image between pulmonary TB without DM and pulmonary TB with DM.

METHODS

This study used a cross-sectional research design. The population in this study were patients with Lung TB without DM and Pulmonary

TB with DM who were at the Siti Khodijah Muhammadiyah Hospital, Sepanjang, Indonesia. The research subjects were taken by consecutive sampling methods according to the inclusion and exclusion criteria. Observations were made by looking at medical record data and chest X-Ray results of pulmonary TB patients, which were then classified according to the degree of severity of the American TB Association (minimal, moderate, and extensive lesions) by three radiology specialists. Data collection and data collection procedures were carried out after obtaining ethical permission from the Siti Khodijah Hospital. After the data was obtained, it was processed by editing, coding, entry, and tabulating, processed, and analyzed using SPSS for chi-square data.

RESULTS

Subject characteristics

Age

Table 1 explains that the lowest TB patients with DM are 41 years old, the highest age is 68 years, and the average age is 56.50 years with a standard deviation of 7.816 years. Whereas in TB patients without DM, the lowest age was 18 years, the highest age was 71 years, and the average age was 42.267 with a standard deviation of 17.656 years.

Table 1

Description of the age of the pulmonary TB patient

TB Patients	Minimal	Maximum	Average	Standard deviation
With DM	41	68	56.500	7.816
Without DM	18	71	42.267	17.656

DM: diabetes mellitus

Sex

Table 2 shows that that 21 patients (70 %) of pulmonary TB patients with DM were male, while 9 other patients (30 %) were female. Meanwhile, 20 patients with pulmonary TB without DM were male (66.7 %), while the other 10 patients (33.3 %) were female. This shows that male patients dominated pulmonary TB patients in this study.

Table 2

Description of the sex of the pulmonary TB patient

Sex	TB Patients with DM		TB Patients without DM	
	n	Percentage	n	Percentage
Male	21	70.0	20	66.7
Female	9	30.0	10	33.3
Total	30	100.0	30	100.0

Degree of Thorax X-Ray

Based on Table 3, it is known that of the 60 patients in this study were dominated by patients with a wide degree of severity, namely 27 people (45.0 %). 21 patients (35.0 %) had moderate Thorax X-Ray severity and 12 (20.0 %) minimum X-Ray severity.

Table 3

Degree of thorax X-Ray in pulmonary TB patients

Degree X-Ray	n	Percentage
Minimal	12	20.0
Moderate	21	35.0
Wide	27	45.0
Total	60	100

Bivariate analysis

Table 4 explains that TB patients without DM who have a thorax X-Ray severity degree of at least 9 patients (30.0 %), moderate as many as 12 patients (40.0 %), and an area of 9 patients (30.0 %). Whereas in TB patients with DM who had a thorax X-Ray severity degree of at least 3 patients (10.0 %), moderate as many as 9 patients (30.0 %), and an area of 18 patients (60.0 %). There was a significant difference in the chest X-ray severity between TB patients without DM and with DM (p=0.040). The contingency coefficient obtained in the analysis results was 0.311. This shows a linear relationship between TB patients with DM by increasing the severity of X-ray thorax. TB patients with DM are at greater risk of having a chest X-ray severity in the form of extensive lesions than TB patients without DM.

Table 4

Difference the chest X-ray between TB patients without DM and with DM

TB Patient	Degree of Thorax X-Ray			Total	p	Contingency coefficient
	Minimal	Moderate	Wide			
Without DM	9	12	9	30	0.040	0.311
	30.0 %	40.0 %	30.0 %	100.0 %		
With DM	3	9	18	30		
	10.0 %	30.0 %	60.0 %	100.0 %		

DM: diabetes mellitus

DISCUSSION

Age-related patient features imply that TB patients with DM are older than TB patients without DM. This is indicated by the average age of TB patients with DM of 56.5 years, while the average age of TB patients without DM is 42.267. In addition, the characteristics based on sex indicate that male patients dominate TB patients with DM and without DM. This is following the literature where men are at greater risk of developing pulmonary TB disease than women. More men smoke and drink alcohol than women, where smoking and alcohol reduce their immunity so that infection is easier, one of which is an infection due to *M. tuberculosis* (17).

The severity of Thorax X-ray is classified into 3 groups including minimal lesions, moderate lesions, and extensive lesions (18). The number of patients in this study who were included in the minimum group was 12 patients (20.0 %), the moderate group was 21 patients (35.0 %), and the wide group was 27 patients (45 %). This suggests that in this study, TB patients were dominated by the severity of chest x-rays with extensive lesions. The severity of the X-Ray Thorax characteristics in patients with pulmonary TB who did not have DM was as follows: minimum lesions in 9 patients (30 %), moderate lesions in 12 patients (40 %), and extensive lesions in 9 patients (30 %). This shows that the severity of X-Ray Thorax patients without DM tends to have a moderate severity of lesions. In pulmonary TB patients with DM, minimal lesions were found in 3 patients (10 %), moderate lesions in 9 patients (30 %), and extensive lesions in 18 patients (60 %). These results indicate that pulmonary TB patients with

DM tend to have a degree of severity in the form of extensive lesions. The results of the tabulation of the severity of the chest X-ray with the group of TB patients without DM and TB with DM showed that TB patients with DM dominated the severity of the broad lesion chest X-ray.

These results are per the literature that the picture of pulmonary TB in DM differs from the picture of pulmonary TB without DM. Pulmonary TB with DM often has an atypical picture. The infiltrates are primarily found in the lower lobes, followed in the middle and some are found in the upper lobes. This is inversely proportional to pulmonary TB without DM, where the infiltrate is more commonly found in the upper part of the lung. Research conducted in India in 2011 found that 10 out of 50 chest X-Ray photos of pulmonary TB patients with diabetes had cavities with a size of more than 2 cm that occurred in the lower lung. Multiple cavities are also often found. This is because DM patients have a decreased immune system (19). Indirectly from the literature, it can be concluded that a history of DM affects the severity of lesions in the lung fields of patients with pulmonary TB.

A report stated that the degree of severity in minimal lesions was found more in patients with pulmonary TB without diabetes, namely 40 % (20). This result is almost the same as the other studies in that the TB lesions in the upper lobe of the lung were 59 %, more than 24 % of TB patients with DM (21). Indirectly, this study proves that the x-ray lesions of the Thorax in pulmonary TB patients with DM are often atypical. The research above indirectly proves that TB patients with DM have a worse degree of X-Ray Thorax severity than TB patients without DM in the form of extensive lesions. The prevalence of pulmonary TB cases in patients with a history of DM occurs in various age groups but has similarities, namely at the old age group, more than 50 years. DM patients accompanied by increasing age will increase the risk of being infected with TB. In addition, DM is more common in old age patients, so it indirectly affects the incidence of pulmonary TB and affects the degree of severity on the radiological image (22).

DM raises the incidence of pulmonary TB; this is supported by biological evidence indicating DM impairs innate and adaptive immune responses, allowing TB to multiply more rapidly. Studies on mice found higher levels of bacteria. In individuals with DM, reduced IFN- and other cytokines production impairs T cell immunity and neutrophil chemotaxis. This plays an essential role in increasing the patient's tendency to become infected with *M. tuberculosis*. The reaction caused by *M. tuberculosis* can induce glucose intolerance and worsen glycemic control in diabetic patients (23). The increased risk of TB in DM patients may be caused by defects in alveolar macrophages or T lymphocytes. A study found an increase in mature alveolar macrophages in pulmonary TB patients, but no significant difference in the number of T cells between pulmonary TB patients without DM and pulmonary TB patients with DM. The decreased proportion of mature alveolar macrophages in TB patients with DM may explain the more severe expansion of lesions in pulmonary TB patients' lung fields (24).

CONCLUSION

There is a significant difference in the severity of X-ray thorax between pulmonary TB patients without DM and pulmonary TB patients with DM; pulmonary TB without DM tends to cause moderate lesions, whereas pulmonary TB with DM tends to cause extensive lesions.

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The importance of health-related to quality-of-life assessment in pulmonary tuberculosis patients: A literature review

La importancia de la evaluación de la calidad de vida relacionada a la salud en pacientes con tuberculosis pulmonar: una revisión de la literatura

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SUMMARY

Introduction: *Pulmonary tuberculosis (TB) has still become a community health problem in the worldwide. TB is a public health threat with significant annual impacts on morbidity and mortality, and a negative impact on overall patients' life. Health-related quality of life (HRQoL) is critical in TB patients, as it is correlated with treatment outcomes and all aspects of the patient's life. This literature review aims to evaluate HRQoL in TB patients and the most affected aspects of it.*

Methods: *Literature studies in online databases such as Google Scholar, PubMed, and journal sites were collected using relevant keywords ("quality of life for pulmonary tuberculosis patients" or "quality of life and health-related tuberculosis" or "quality of life evaluation for pulmonary tuberculosis).*
Results: *Psychological or mental aspects affect the quality of life because they are the main aspect of a person to recognize themselves and the environment and decide what action needs to be taken in a patient with pulmonary tuberculosis. In this case, will have an impact on the continuity of extended therapy and the need to be disrupted routine control. This can result in successful treatment for the normal six months. For this reason, every aspect of life in TB patients is interrelated, especially the physical and mental aspects that play a role in determining HRQoL.*
Conclusion: *Although many factors affect HRQoL aspects in TB patients, the psychological aspect is the most influential.*

Keywords: *Health-related quality of life, tuberculosis patients, mental health, and physical health.*

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RESUMEN

Introducción: *La tuberculosis pulmonar (TB) se ha convertido en un problema de salud comunitaria en todo el mundo. La TB constituye una amenaza para la salud pública con un impacto anual significativo en la morbilidad y la mortalidad, y un impacto negativo*

en los aspectos generales de la vida de los pacientes. La calidad de vida relacionada con la salud (CVRS) es fundamental en los pacientes con tuberculosis (TB), ya que se correlaciona con los resultados del tratamiento y con todos los aspectos de la vida del paciente. Esta revisión de la literatura tiene como objetivo evaluar la CVRS en pacientes con TB y los aspectos más afectados de la misma.

Métodos: *Se recopilaron estudios de literatura en bases de datos en línea como Google Scholar, PubMed y sitios de revistas utilizando palabras clave relevantes ("calidad de vida para pacientes con tuberculosis pulmonar" o "calidad de vida y tuberculosis relacionada con la salud" o "evaluación de la calidad de vida para tuberculosis pulmonar).*

Resultados: *Los aspectos psicológicos o mentales afectan la calidad de vida, debido a que son los principales aspectos para que una persona se reconozca a sí misma y al entorno y decida qué acciones se deben tomar en un paciente con tuberculosis pulmonar. En este caso, tendrá un impacto en la continuidad de la terapia prolongada y la necesidad de interrumpir el control de rutina. Esto puede resultar en un tratamiento exitoso durante los seis meses normales. Por esta razón, todos los aspectos de la vida de los pacientes con TB están interrelacionados, especialmente los aspectos físicos y mentales que juegan un papel en la determinación de la CVRS.*

Conclusión: *Aunque muchos factores afectan los aspectos de la CVRS en los pacientes con TB, el aspecto psicológico es el que más influye.*

Palabras clave: *Calidad de vida relacionada con la salud, pacientes con tuberculosis, salud mental y salud física.*

INTRODUCTION

Tuberculosis (TB) is still considered the most complex disease in the world since the number of cases increases every year (1,2). The World Health Organization (WHO) estimates that 8.6 million new cases of TB occur each year. Extrapulmonary TB accounts for around 15 % to 20 % of all TB cases and more than 50 % of TB cases in HIV-positive patients (3). There are still many problems found in preventing TB including lack of knowledge (4) and resistance to drugs such as rifabutin (5).

The number of morbidities and mortalities caused by TB has escalated in all countries worldwide (6,7). This number has made TB a public health threat and global emergency disease (8). Addressing the number of these cases, WHO has a policy of global action plan to reduce the number of morbidity around the world through Millennium Development Goals (MDGs) 2015 (9,10) followed by Sustainable Development Goals policy (SDGs) 2030 (11,12). In Indonesia, the number of TB cases increased between 2013 – 2016, in which the incidence rate was 391 cases per 100 000 population. The number of new TB cases in Indonesia was as many as 420 994 cases in 2017 (data as of May 17, 2018) (4).

This policy has been agreed upon and implemented throughout the world. However, the mortality and morbidity caused by TB remain high. It was reported that in 2017, TB reached 10 million cases, and the mortality rate was estimated at 1.6 million (13). High morbidity and mortality rate is related to treatment programs, which is also one of this disease's problems. This is because there are still high rates of non-compliance with medication in TB patients. This non-compliance behavior is mainly due to the patients' lack of motivation. Another cause is the level of knowledge; in this case, a person's level of knowledge is related to the adherence to the intake of anti-tuberculosis drugs (14).

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis (M. tuberculosis)*. This bacteria is an acid-resistant bacteria (15,16) due to its morphology and cell wall structure, which is rich in lipids and wax (17) *M. tuberculosis* is an intracellular pathogen that can survive for an extended period in macrophages (18). *M. tuberculosis*' ability to cause disease is entirely dependent on macrophage apoptosis during infection. Under their many capabilities and capacity for immunological monitoring, the elimination of cellular debris, microbial clearance, and the resolution of inflammation, pulmonary macrophages play essential roles in the initial innate immune response (19). *M. tuberculosis* can infect any area of the body, although it most frequently infects the lungs, causing pulmonary TB (15). According to data, untreated pulmonary TB might result in respiratory complications (20).

Besides its high morbidity and mortality rate, duration of treatment and its combination could make differences in TB patients' quality

of life. Nevertheless, six months after, quality of life (QoL) psychiatric treatment is still at a low level (10). Studies suggest that QoL surveys of pulmonary TB patients can affect the QoL of patients both physically and mentally (21). Without proper rehabilitation, TB patients will tend to have more disability, lower quality of life, and higher mortality rate (22). Therefore, it is necessary to evaluate the QoL in TB patients (13). This evaluation can help to estimate patients' conditions during and after therapy. Evaluation is an important matter because it can affect the result of pulmonary TB patients' life aspects (23).

Studies have shown that there are many factors related to the impact of tuberculosis on health-related quality of life (HRQoL) TB patients, such as sociodemographic factors (age, employment, household, knowledge, and gender) and QoL aspect itself such as physical, mental, social, and environment (24), being the physical and mental aspects the most affected aspect of all.

The study in Malaysia states that there is a QoL reduction in the physical health aspect which is not restored as originally (24). The study in Brazil demonstrated that psychological problems such as depression and anxiety disorders; this caused no improvement in psychological aspect value at each phase and continued to the final therapy (2). A good evaluation must be done so that therapy focus is consistent in physical and mental patients to improve the QoL in tuberculosis patients' (24,25). This literature review aims to determine the aspects of HRQoL in pulmonary tuberculosis patients and the factors that cause it.

METHODS

Secondary data is collected both from online sites and offline. The data obtained are literature books, scientific articles, and scientific journals that are formulating the problem. Literature studies were searched by using relevant keywords ("tuberculosis", "health-related quality of Life", "pathophysiology","physic and mental aspect"), through online databases such as Google Scholar and PubMed and the address websites of the relevant journal. The journals chosen were journals from 2010 to 2020 with the minimum publication category indexed by Scopus and SINTA 4. The exclusion criteria are journals not indexed by Scopus or SINTA 4, and then data is analyzed with bibliographic annotation analysis. Bibliographic annotation can be summarized as a list of sources used in a study, with a conclusion associated with each source.

RESULTS

In Table 1 are listed the articles used for this review. Based on existing studies, 9 out of 12 works of the literature showed that the mental aspect is the most affected in patients with pulmonary tuberculosis. In addition, emotional support also helps pulmonary tuberculosis patients live their daily lives well, affecting scores on a better mental aspect. Most studies also mention that physical aspects affected TB patients. In some studies, the physical aspect showed a great improvement after TB treatment. Another aspect that was also influenced by pulmonary TB was the patient's general health. This aspect was reduced when patients were diagnosed with pulmonary TB. Two studies showed that patient's general health remained poor even after TB therapy regimens were given.

DISCUSSION

According to WHO, QoL is an individual's perception of a person's lifestyle, individual existence, and relationship to life goals, expectations, standards, and concerns. QoL's problem is commodious and complex. This includes physical health, psychology, self-reliance level, social relation, and environment where they belong (36,37). HRQoL is a concept that impacts someone's physical and mental health (36). When patients have a psychological and physical problem, it can be said that they have low QoL due to health definition is mental health and physical health (38).

Many QoL evaluation instruments have identical evaluated aspects. Generic measurement can be used in almost all populations, regardless of the underlying condition or disorder. In 1996, WHO released an instrument evaluation to evaluate HRQoL called World Health

Table 1

Bibliographical Annotation Analysis in Journals about Health-Related Quality of Life Tuberculosis Pulmonary

Study	Year	Country	Instrument	Rated Aspect	Time	Result
Louw (25)	2012	South Africa	SF-12	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, Sociodemographic	After 6-month treatment	In the physical aspect, there was an increase in value and was significant. Psychological stress has a negative impact on the physical and mental aspects of the patient.
Kittikraisak (26)	2012	Thailand	EQ-5D	Quality of Life: aspects of mobility, self-care, habitual activities, pain or comfort, and anxiety/depression, as well as sociodemographic	Variable	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, Sociodemographic
Atif (24)	2014	Malaysia	SF-36	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, Sociodemographic	Start Treatment, End of Intensive phase, and end of Treatment	Physical component summary (PCS) and Mental component summary (MCS) have low values because they are below the standard value <47 Norm-based scorings (NBS). This still happened until the end of therapy, although there was an increase in the value at each treatment phase. Depression risk occurs in the early phases of treatment.
Dasa (27)	2019	Ethiopia Timur	PHQ-9	Sociodemographic dan condition, Depression	One month after the intensive phase	Age, income, new TB patients, and patients in the first 3 months of treatment were all associated with psychological aspects of depression.
Abrham (28)	2018	Ethiopia Timur	SF-36v2	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, Sociodemographic	After Treatment	The general health aspect has the worst quality of life-related to health compared to other aspects.
Shahdadi (29)	2018	Iran	SF-36	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role	On Treatment	Physical and mental aspects have improved. However, the mental aspect has a lower value than the physical aspect. Some factors influence this value, namely family status, income, and educational status.
Zarova (30)	2018	Zimbabwe	MSPSS, EQ-5D	Quality of Life: aspects of mobility, self-care, habitual activities, pain or comfort, and anxiety/depression, as well as sociodemographic	On Treatment	The mental aspect improves when the patient gets support.

Continue on page S458…

…continuation Table 1.

Study	Year	Country	Instrument	Rated Aspect	Time	Result
Kisaka (31)	2016	Uganda	SF-36	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, Sociodemographic	Before Treatment, Intensive phase, and Advanced phase	Before therapy, the general health aspect was the lowest and the mental health aspect the highest. The aspects of mental health and physical health have improved in each phase. At the start of treatment, patients with informal employment were associated with decreased HRQoL, patients with unmarried status had good HRQoL, patients with social status in an economically related society were able to have better HRQoL than patients with low economic status. Increasing age can reduce HRQoL.
Dos Santos (2)	2017	Brazil	SF-36, HADS, WHOQOL-HIV Compared Brazilian Number Score	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, (Vital), Emotional Role, Sociodemographic and depression	when diagnosing TB	All aspects scored lower under the Brazilian Norm Score (BNS). More than 1/3 of patients have depression or anxiety. Tuberculous patients have poor HRQoL, and many patients experience depression and loss. Several aspects of this study reported that aspects of body pain, general health, social functioning, emotional roles, and mental health were significantly reduced in patients with possible patient reports without the possibility of anxiety. For example, depression causes the patient to smoke, which is related to the psychological aspects of the patient.
Abdulelah (32)	2016	Iraq		Physical well-being, social and economic well-being, emotional well-being/living, functional well-being, spiritual well-being	Start treatment or baseline, end of the intensive phase, and end of TB treatment	After two months of intensive care, physical and functional aspects have improved. At the end of therapy, health-related quality of life health was significant in all aspects
Jaber (33)	2016	Yaman	SF-36	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, Sociodemographic	Initial Treatment, End of Intensive Phase, End of Advanced Treatment	At the start of therapy, the physical and mental aspects were still below standard (47–53 normal based score (NBS)). In the final intensive phase, improvement was found but the score was still below the research standard (47–53 normal based score (NBS)). In the final phase of treatment, the physical aspect increased above the NBS score and the mental aspect increased slightly, which means that the patient was mentally depressed until the end of treatment because the score was below the NBS standard (47–53 normal based score (NBS)).

Continue on page S459…

…continuation of Table 1.

Study	Year	Country	Instrument	Rated Aspect	Time	Result
Dar (34)	2018	India, Kashmir	WHOQOL-BRIEF	Physical health, mental health, psychological health, social and environment	Initial Treatment and End of Intensive Phase	In the initial phase of treatment, the quality of life is low in physical aspects, followed by psychological, social, and environmental relationships. At the end of the intensive phase, there was an increase in several aspects, especially psychological aspects whose scores were higher than other aspects but were not significantly high, and social aspects did not experience any improvement in value.
Wahyuni (35)	2018	Indonesia	SF-36	General health, Bodily Pain, Physical Function, Physical Role, Social Function, Mental Health, Energy and Fatigue (Vital), Emotional Role, Sociodemographic	End of Intensive Phase	In this study, it was found good scores on aspects of pain and aspects of physical function. Meanwhile, the lowest quality of life for pulmonary TB patients is the aspect of general health followed by the emotional role aspect.

Note: SF-36 (Short Form 36), NBS (Normal Brazilian Scores), PCS (Physical Component Summary), PHQ-9 (Patient Health Questionnaire-9), SF-12 (Short Function 12), SF-36v2 (Short Form 36 version 2), VAS (Visual Analog Scale), WHOQOL-BREF (WHO-Quality of Life-BREF), WHOQOL-HIV (World Health Organization-Questioner of Life-HIV), HADS (Hospital Anxiety and Depression Scale), FACIT-TB (Instrument Functional Assessment of Chronic Illness Therapy TB), EQ-5D (Europe Questioner 5 Domain), HRQoL (Health-related quality of life), MCS (Mental Component Summary), NBS (norm-based scoring, MSPSS (Multidimensional Scale of Perceived Social Support).

Organization-Questioner of Life (WHOQoL), which consists of four aspects: the measurement domain as 4 aspects of QoL (39). Another evaluation instruments are Short-Form 36 (SF-36). This instrument is often used to evaluate QoL in tuberculosis patients (13,40) SF-36 measured two aspects. There are physical and mental dimensions (41). The research conducted in Shanghai, China, stated that SF-36 is a questioner used internationally and already proved the validity and reliability (42).

There is also Europe Quality-5 Domain (EQ-5D), an instrument that is often used in Europe. This instrument has two parts. The first part is health status descriptions, and the second part is Europe Quality-Visual Analog Scale (EQ-VAS), a visual analog scale about the present condition (13,26,43). Another instrument is Short Form 12 (SF-12), a short form representative for SF-36. The difference is in the number of questions. Hospital Anxiety and Depression Scale (HADS) is the instrument that used by psychiatric to measure patients' anxiety, depression, and psychological aspect, which can impact QoL in tuberculosis patients.

There are many factor or aspect which related with QoL in pulmonary TB patients like a financial problem during diagnosis and treatment, successful or failed anti-tuberculosis therapy, the detrimental effect of anti-tuberculosis, value deflation after the final treatment, congenital disease, HIV infections, economic status, demography factor such as age and gender, disease symptoms and functional limitation due to disease, stigma, and ex-communication from society after tuberculosis diagnosed and emotional and anxiety disorder (13). There is also a perception in society that tuberculosis patients can infect the disease environment. This social problem can impact the psychological aspect (8,44).

Research in Ethiopia stated that the physical aspect has a high value in affecting health-related to QoL patients (13,27,28). TB sufferers tend to change their behavior because of feeling isolated by their environment. The environmental stigma against TB sufferers also causes depression (2). This can evoke anxiety in TB patients and interfere with their psychological aspect (2,24,30,33). Studies in Pakistan show that depression in TB patients does not improve until the final treatment phase. The study also stated that TB patients who were undergoing treatment had a high association with depression, anxiety, and other psychological problems (43).

Low education levels and bad social, economic status can make a deflation QoL (13). Education level influences knowledge about tuberculosis and has an impact on research value. People who go to school have more knowledge about tuberculosis than people who do not attend school (45). Several studies stated that a lack of knowledge about tuberculosis and its therapy causes anxiety and frustration (10,21). A study in Zimbabwe stated that low education level gives a bad influence on mental health (30) in concordant with a study in Indonesia, also found that education level can impact knowledge about TB and has patients' QoL (45).

Most patients with TB cannot work to earn a living (25) and they may have a financial burden due to medical expenses and the possibility of losing their jobs due to the disease (13,27). Low income also causes psychological pressure and depression because of the inability to fill up individual and household demands (13,25). Another study in Ethiopia showed that low financial levels could affect the quality of life and patients' psychological condition.

Comorbid factors in TB patients also have a terrible impact on QoL. A study in India stated that patients with comorbid diabetes mellitus would have bad QoL than TB patients without the comorbid disease (13). Another study stated that TB patients with HIV disease (TB-HIV) experienced an improvement in recovery, but no significant changes were found in these patients (8).

In addition, failure of TB treatment can affect their psychological aspects, because they have to start the treatment phase from the beginning, intensive treatment, and follow-up treatment for 8 months (8,44). The duration of tuberculosis therapy escalates anxiety conditions and depression, which cause indolent manner for medicine intake, this also creates a risk for tuberculosis multidrug resistance or TB-MDR (46). A study in Indonesia states that significant family factors influence the QoL among pulmonary TB patients through promoting successful treatment, social support, and recovery (47). In society, TB-MDR patients get more stigma and discrimination from huge society, even though the patients belong to a high social class (28,48).

CONCLUSION

The most influential aspect of HRQoL in TB patients is the psychological aspect of TB disease's such as psychological pressure, social stigma, fear of disease, and lack of support from surroundings cause deflation of QoL patients. Intensive treatment and evaluation in every phase of treatment are necessary to make a maximal therapy on tuberculosis patients, especially in Indonesia.

Conflicts of Interest

The authors declare no conflict of interest.

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ARTÍCULO ORIGINAL

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Correlation of pre-operating antibiotic types with surgical site infection in post-appendectomy patients

Correlación de tipos de antibióticos previos a la operación con infección en el lugar quirúrgico en pacientes pos-apendectomía

Fitria Romadoni[1*], Handayani[2*•], Aditya Bhayusakti[3*]

SUMMARY

Introduction: *Prophylactic antibiotics are antibiotics given to patients undergoing surgery to prevent infection due to surgery. Surgical site infection (SSI) is an infection that occurs when microorganisms from the skin, other body parts, or the environment enter the postoperative incision. This study aimed to analyze the relationship between preoperative antibiotics and the occurrence of SSI.*
Methods: *This study used cross-sectional and analytical observational research design. Secondary data collection from medical records of appendectomy surgery patients with a history of antibiotic use at Jemursari Islamic Hospital, Surabaya, Indonesia in 2017-2019 was used.*
Results: *Of the 138 subjects, the antibiotics used were 128 (93 %) cephalosporins and 10 (7 %) metronidazole. In the cephalosporin type, ceftriaxone was the most widely used antibiotic (95/128, 74.2 %). The incidence of SSI in patients after appendectomy was six patients (8 %), while 132 patients (92 %) did not experience SSI. Of 128 patients given cephalosporin prophylactic antibiotics, 122 patients (95.3 %) did not experience SSI, and six patients (4.7 %) experienced SSI after appendectomy. Meanwhile, in 10 patients who were given metronidazole prophylactic antibiotics, it was found that all (100 %) did not have SSI. Statistical analysis showed no relationship between the type of pre-operative antibiotics and the occurrence of SSI (p=1).*
Conclusion: *Pre-operative administration of antibiotics can prevent the occurrence of SSI in patients after appendectomy.*

Keywords: *Prophylactic antibiotics, surgical site infection, appendicitis, appendectomy.*

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RESUMEN

Introducción: *Los antibióticos profilácticos son antibióticos que se administran a pacientes sometidos a cirugía para prevenir la infección debido a la cirugía. La infección del sitio quirúrgico (ISQ) es una infección que se produce cuando los microorganismos de la piel,*

otras partes del cuerpo o el medio ambiente ingresan a la incisión posoperatoria. Este estudio tuvo como objetivo analizar la relación entre los antibióticos preoperatorios y la aparición de ISQ.

Métodos: *Este estudio utilizó un diseño de investigación observacional transversal y analítico. Se utilizó la recopilación de datos secundarios de los registros médicos de pacientes sometidos a cirugía de apendicectomía con antecedentes de uso de antibióticos en el Hospital Islámico Jemursari, Surabaya, Indonesia, en 2017-2019.*

Resultados: *De los 138 sujetos, los antibióticos utilizados fueron 128 (93 %) cefalosporinas y 10 (7 %) metronidazol. En el tipo de cefalosporina, la ceftriaxona fue el antibiótico más utilizado (95/128, 74,2 %). La incidencia de ISQ en pacientes después de la apendicectomía fue de seis pacientes (8 %), mientras que 132 pacientes (92 %) no experimentaron ISQ. De 128 pacientes que recibieron antibióticos profilácticos con cefalosporinas, 122 pacientes (95,3 %) no experimentaron ISQ y seis pacientes (4,7 %) experimentaron ISQ después de la apendicectomía. Mientras tanto, en 10 pacientes que recibieron antibióticos profilácticos con metronidazol, se encontró que todos (100 %) no tenían ISQ. El análisis estadístico no mostró relación entre el tipo de antibióticos preoperatorios y la aparición de ISQ (p= 1).*

Conclusión: *La administración preoperatoria de antibióticos puede prevenir la aparición de ISQ en pacientes después de una apendicectomía.*

Palabras clave: *Antibióticos profilácticos, infección del sitio quirúrgico, apendicitis, apendicectomía.*

INTRODUCTION

Appendicitis is the most common significant surgical disease. Although appendicitis can occur at any age, it is most common in adolescents and young adults. The mortality rate of this disease was high before the era of antibiotics. For the management of appendicitis, the most appropriate action and the only best option is surgery (appendectomy) (1,2). According to data released by the Indonesian Ministry of Health in 2010, the incidence of appendicitis in Indonesia was 621 435 people, with a percentage of 3.53 % (3). Appendicitis is the second-highest non-communicable disease in Indonesia in hospitalization in 2009 and 2010 (4). Based on initial data on patients with appendicitis surgery (appendectomy) at the Jemursari Islamic Hospital, Surabaya, Indonesia, in 2017-2019, there were 240 cases of patients with all patients undergoing preoperative antibiotics.

Surgical site infection (SSI) is one of the post-abdominal surgery complications and nosocomial infections in surgical patients. A survey by the World Health Organization shows that 5 %-34 % of the total nosocomial infections are SSI (5). Factors for the incidence of SSI from patients, for example, are diabetes mellitus (DM), obesity, severe malnutrition, and the wound's location. While the operating factor, for example, is the length of the operation and the operating procedure. Gram-negative bacteria are the dominant cause of SSI, especially in general surgery, neurosurgery, bone surgery, and others (6). The surgical wound is said to be infected if the wound oozes pus and signs inflammation. SSI found the fastest is on the third day and the most found on the fifth day, and the longest is the seventh day (7).

Appendectomy is the most efficient way of treating appendicitis, with a success rate of >95 % and a low overall morbidity and mortality rate (8). Factors that play an essential role in influencing the incidence of SSI are endogenous and exogenous. In terms of age, old age is associated with many structural and functional changes that make the skin and subcutaneous tissue more susceptible to infection (9).

Prophylactic antibiotics are antibiotics used for patients who have not been infected with an infection but are suspected of having a high chance of getting it, or if they are exposed to infection, it can harm the patient. The most widely used prophylactic antibiotics are cefazolin and ceftriaxone (10). Previous research showed that the type of antibiotic therapy and prophylaxis most widely used in surgical cases of appendicitis was ceftriaxone by 65.28 % (11,12).

In a study at Dr. Kariadi General Hospital, Semarang, Indonesia, six samples (35.2 %) of appendectomy laparotomy patients with SSI signs were given the antibiotic ceftriaxone. In appendectomy laparotomy, patients with SSI signs were given non-ceftriaxone antibiotics, 1 sample (5.8 %). Meanwhile, in patients with laparoscopic appendicectomy with SSI signs who were given ceftriaxone antibiotics, two samples (14.2 %) did not find any signs of SSI in laparoscopic appendectomy patients who were

given non-ceftriaxone antibiotics. The treatment for the SSI is that the wound must be cleaned and treated so that it does not spread and the wound can recover (7,13). The purpose of this study was to analyze the relationship between preoperative antibiotics and the occurrence of SSI in patients after an appendectomy at Jemursari Hospital Surabaya, Indonesia.

METHODS

This type of research is analytic observational with a cross-sectional design. The population in this study was the medical records of inpatient appendectomy at Jemursari Islamic Hospital, Surabaya, Indonesia, in 2017-2019, amounting to 240 patients. The number of samples was calculated using simple random sampling and obtained as many as 150 subjects. However, due to research limitations, the sample became 138 subjects.

The sample of this study was medical records of appendectomy patients with a history of pre-operative antibiotic use in January 2017 - December 2019 with inclusion and exclusion criteria. The inclusion criteria in this study were a diagnosis of acute appendicitis, post-appendectomy patients aged 17-45 years, a history of pre-operative antibiotic use, and the patient was a control patient. At the same time, the exclusion criteria for this study were patients with appendicitis without surgery and patients who died after appendectomy.

This research was conducted at Jemursari Islamic Hospital, Surabaya, Indonesia. The time of the study started from September 2019 to August 2020. The independent variable in this study was the use of preoperative antibiotics for appendicectomy. At the same time, the dependent variable was the occurrence of SSI in patients after appendectomy. This research instrument used secondary data: medical record data of appendectomy patients with a history of preoperative (prophylactic) antibiotic use at Jemursari Islamic Hospital, Surabaya, Indonesia, in 2017-2019. The procedure of this research was after getting data from medical records, editing, coding, tabulating, entry, and cleaning are carried out. The data were then analyzed using Chi-Square. This research had passed the code of ethics test at Jemursari Islamic Hospital Surabaya, Indonesia, with the Ethics number 0148/KEPK-RSI JS/11/2020.

RESULTS

The sample characteristics in this study were described based on diagnosis, age, type of preoperative antibiotics, SSI occurrence, and control patients. Of the 138 study subjects, almost all (93 %) of appendicectomy patients used cephalosporin prophylactic antibiotics. The types of prophylactic antibiotics in appendectomy patients are described in Table 1 as follows.

Table 1

Types of prophylactic antibiotics used

Types of antibiotics	n	%
Cephalosporins	128	93
Metronidazole	10	7
Total	138	100

As many as 128 types of cephalosporin antibiotics were used, most of them (74.2 %) using ceftriaxone cephalosporins. The types of cephalosporin antibiotics used are described in Table 2. The results showed that six patients (8 %) after appendectomy experienced SSI, and almost all 132 patients (92 %) did not experience SSI.

Table 2

Types of cephalosporin antibiotics used

Cephalosporin type	n	%
Cefuroxime	24	18.60
Ceftriaxone	95	74.2
Cefazolin	2	1.6
Cefoperazone	5	4
Cefotaxime	1	0.80
Cefepime	1	0.80
Total	128	100

Based on Table 3, the Chi-square statistical test results using the SPSS statistical application showed a significant p-value of 1.00 (>0.05), indicating no significant relationship between the antibiotic and the occurrence of SSI in patients after appendectomy. Of the 128 patients given cephalosporin prophylactic antibiotics, almost all (95.3 %) of patients after appendectomy did not experience SSI, and a small proportion (4.7 %) of patients after appendectomy had SSI. Meanwhile, in 10 patients given metronidazole prophylactic antibiotics, all (100 %) did not experience SSI.

Table 3

Crosstabulation of types of antibiotics with the occurrence of infection

Types of Prophylactic Antibiotics	Post operation						p
	Infected		Not infected				
	n	%	n	%	n	%	
Cephalosporins	6	4.7	122	95.3	128	100	1.00
Metronidazole	0	0	10	100	10	100	(>0.05)

DISCUSSION

The majority of post-appendectomy patients do not have SSI. The statistical tests showed no significant relationship between the type of pre-operative antibiotics and the occurrence of SSI in post-appendectomy patients. Previous studies have shown no relationship between the type of irrational use of prophylactic antibiotics and the incidence of SSI. Surgical patients with irrational use of antibiotics do not have SSI due to prophylactic antibiotics given with a broader spectrum that can include gram-positive and negative bacteria and the use of antibiotics with a longer duration, which can prevent bacterial contamination in the treatment room (14). In another study, prophylactic antibiotics were given more use to third-generation cephalosporins, especially broad-spectrum Ceftriaxone, because of concerns about first-generation antibiotic resistance, bacterial patterns in the operating room, and treatment. The use of prophylactic antibiotics in the preoperative period aims to tackle infection so that the postoperative risk can be reduced as low as possible so that the provision of prophylactic antibiotics can minimize SSI (15).

The most widely used type of prophylactic antibiotic in patients after appendectomy is Ceftriaxone. The results of this study are following research that has been done that the type of antibiotic therapy and prophylaxis that is most widely used in cases of surgical appendicitis is Ceftriaxone (12,16). In addition to being used in cases of surgical appendicitis, a study showed that prophylactic antibiotics were 98 % effective in cesarean section (17). The reason Ceftriaxone is most widely used is possible because, in addition to the advantages of using cephalosporins in general, it also has a long half-life of up to 8 hours with a dose of 1 gram/injection, so that if the operation lasts a long time, it is not necessary to increase the dose of Ceftriaxone during surgery. Previous research also shows that prophylactic antibiotics in appendectomy surgery with indications of appendicitis used in Surakarta, Indonesia, are third-generation cephalosporins such as Ceftriaxone and cefotaxime (18).

Most of the antibiotics used were third-generation cephalosporins, as many as 235 (66.2 %) patients, carbapenem as many as 54 (15.2 %) patients, and penicillin 41 (11.5 %) patients (19). The 3rd generation cephalosporin that is widely used is ceftriaxone, and there is a relationship and influence between the nature

of the operation, type of antibiotic, time of administration, and duration of operation with SSI with a p-value < 0.05 (20,21). There are differences in the results from previous studies due to the number of samples and the number of different types of antibiotics affecting the p-value of the statistical test results.

This study shows that the incidence of SSI is relatively low. This is in line with previous research that there were 7 (0.55 %) SSI cases out of 1,281 surgical procedures performed at hospitals in Surabaya, Indonesia, in 2012 (22). Emphasis on risk factors is very influential on the incidence of SSI, one of which is cleanliness and type of procedure. Risk factors that influence the incidence of SSI in clean-contaminated surgery patients include preoperative bathing and shaving (23). Following previous studies, the prevalence of SSI in Indonesia is estimated at around 2.3 %-18.3 % and is the most common nosocomial infection. Appendectomy is included in the category of clean surgery contamination. The possibility of SSI in this operation ranges from 5 %-15 % (18,19).

There are limitations to this study. This study uses the simple random sampling technique by taking data from medical records. Much static is included in the exclusion criteria so that the data needed is less so that it needs to be re-stated, and the research time is less efficient. A preliminary diagnosis is written not to be used in research, such as not writing down the type of appendicitis such as perforated appendicitis, acute appendicitis, and chronic appendicitis. Writing a diagnosis after control is also incomplete to determine the presence of infection or not. Then the time of the study coincided with the Coronavirus Disease 2019 (COVID-19) pandemic, so researchers had to postpone the time of data collection.

CONCLUSION

The types of antibiotics used in appendectomy patients are mostly cephalosporin (Ceftriaxone) prophylactic antibiotics. There was no significant relationship between the type of preoperative antibiotics and the occurrence of SSI in patients after appendectomy. Preoperative antibiotics can prevent the occurrence of SSI.

Conflicts of Interest

The authors declare no conflict of interest.

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Respiratory allergy with concentration ability in young adults

Alergia respiratoria con capacidad de concentración en adultos jóvenes

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SUMMARY

Introduction: *Respiratory allergies prevalence in Indonesia, Asia, and the world ranges from 4-10 %. Patients with respiratory allergies and other chronic respiratory diseases often experienced deterioration of productivity and concentration ability. This study aims to observe the correlation between respiratory allergy and concentration ability in adults.*
Methods: *The design of the study was retrospective observational. 18-25 years old participants with or without a respiratory allergy were included. The Respiratory Allergy Prediction Test (RAPt) questionnaire was used to collect respiratory allergy data. At the same time, the Krawietz Concentration Scale questionnaire was used to measure concentration ability.*
Results: *There were 149 subjects in this study, with the female proportion was 101 (67.79 %), and the male was 48 (32.21 %). The mean age of the subjects was 19.30 ± 0.96 years. The result of this study indicated that there was no significant correlation between respiratory allergy (RAPt ≥ 1) with reading and listening focus (RLF) and (p= 0.231), control of focus before sleep (CFBS) (p= 0.544), RLF-CFBS (p= 0.524), and concentration ability (p= 0.538). However, there was a tendency between respiratory allergy (RAPt ≥ 1) and uncontrolled focus (p= 0.070; CI 90 %; power 55.60 %), and there was also a significant correlation between respiratory allergy (RAPt ≥ 3) and concentration ability (p= 0.029; CI 95 %; power 59.84 %).*
Conclusion: *Respiratory allergy patients can perform types of work that require high concentrations only if their RAPt result is less than 3.*

Keywords: *Respiratory allergy, concentration ability, Krawietz concentration scale questionnaire, respiratory allergy prediction test questionnaire.*

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RESUMEN

Introducción: *La prevalencia de alergias respiratorias en Indonesia, Asia y el mundo varía entre el 4 % y el 10 %. Los pacientes con alergias y otras enfermedades respiratorias crónicas a menudo experimentaron un deterioro de la productividad y la capacidad de concentración. Este estudio tiene como objetivo observar la correlación entre la alergia respiratoria y la capacidad de concentración en adultos.*
Métodos: *El diseño del estudio fue observacional retrospectivo. Se incluyeron participantes de 18 a 25 años con o sin alergia respiratoria. Se utilizó el*

cuestionario de la Prueba de predicción de alergias respiratorias (RAPt) para recopilar datos sobre alergias respiratorias. Al mismo tiempo, se utilizó el cuestionario Krawietz concentration scale para medir la capacidad de concentración.

Resultados: *Hubo 149 sujetos en este estudio, la proporción de mujeres fue de 101 (67,79 %) y la de hombres fue de 48 (32,21 %). La edad media de los sujetos fue de 19,30 ± 0,96 años. El resultado de este estudio indicó que no había una correlación significativa entre la alergia respiratoria (RAPt ≥ 1) con el enfoque de lectura y escucha (RLF) dan (p= 0,231), control de enfoque antes del sueño (CFBS) (p= 0,544), RLF -CFBS (p= 0,524) y capacidad de concentración (p= 0,538). Sin embargo, hubo una tendencia entre la alergia respiratoria (RAPt ≥ 1) y el enfoque descontrolado (p= 0,070; IC 90 %; potencia 55,60 %), y también hubo una correlación significativa entre la alergia respiratoria (RAPt ≥ 3) y la capacidad de concentración (p= 0,029; IC 95 %; potencia 59,84 %).*

Conclusión: *Los pacientes con alergia respiratoria pueden realizar tipos de trabajo que requieren altas concentraciones solo si su resultado de RAPt es inferior a 3.*

Palabras clave: *Alergia respiratoria, capacidad de concentración, cuestionario de la escala de concentración de Krawietz, cuestionario de la prueba de predicción de alergia respiratoria*

INTRODUCTION

Respiratory allergies are allergies in the airways that include allergic rhinitis and bronchial asthma (1). The prevalence of respiratory allergy cases in Indonesia, Asia, and the world ranges from 4 %-10 % (2-4). The diagnosis of respiratory allergy is confirmed by skin prick test (SPT) and provocation tests with certain allergenic substances and examination of IgE levels and other molecular tests (1).

Allergic rhinitis (AR) is an inflammatory disease of nasal mucosa caused by immunoglobulin E (IgE), especially after exposure to allergens. RA affects 10 to 20 % of the total population, and this number is increasing steadily. The severity of allergic rhinitis can be measured subjectively by calculating the total nasal symptom score (TNSS) and objectively by calculating serum IgE levels. Moderate to severe AR can affect the quality of life of patients and is found in 67.5 % of all AR patients (5). The main symptoms of AR are sneezing, stuffy nose, itchy nose. Symptoms in eyes, ears, and throat postnasal drip are also seen in some cases (6).

While rhinosinusitis is inflammation of nasal mucosa and paranasal sinuses, one of the predisposing factors for rhinosinusitis is allergic rhinitis, and both of them have a multifactorial relationship. The incidence of acute rhinosinusitis in adults is 2-5 times a year and 7-10 times a year in children (7).

Allergic conditions, allergic asthma, and airway hyperreactivity (AHR) are known as risk factors for chronic obstructive pulmonary disease (COPD) (8). COPD is a non-communicable disease that remains become a health problem in Indonesia. The morbidity and mortality rates of COPD patients are associated with periodic exacerbations and decreased lung function. Other problems that are commonly seen in COPD patients are depression, isolation, and weight loss (9).

Patients with respiratory allergies such as allergic rhinitis, bronchial asthma, and other chronic respiratory diseases such as COPD and rhinosinusitis often experienced a deterioration in work productivity, for about 35.8 ± 27.56 % (4). A study shows that people with respiratory allergies in Asia Pacific experience decreased work productivity by up to 36 %. Decreased concentration can result in decreased work ability visually and auditory (10). Another study has shown that work concentration decreases in patients with allergic rhinitis after a nasal provocation test is performed (11). Patients with respiratory allergies in the Asia Pacific also have a low quality of life. Most asthma patients have a Mini Asthma Quality-of-Life Questionnaire (miniAQLQ) score of 4.8 ± 1.20 (range 1-7) (4). In addition, allergic conditions tend to increase concentration disorders such as attention-deficit hyperactivity disorder (ADHD) in children (12). ADHD is a common neurobiological disorder in primary school-age children. The main symptoms of ADHD are hyperactivity, inattention, and impulsivity. If left untreated, ADHD children will have social, educational, or work problems in their community due to the severity of the symptoms (13).

Nasal congestion symptoms in allergic conditions will negatively impact the overall

quality of life, including the patient's physical and emotional condition. Generally, people with an allergy will experience reduced productivity, difficulty concentrating, decreased time and quality of rest, fatigue, and can be stress triggering factors (14). In addition, respiratory allergies increase cholinergic response and decrease the beta-adrenergic response, thereby decreasing the activity of the reticular activating system (RAS) (12,15). A decrease in RAS activity is accompanied by declining in reaction timeliness and a further decrease in concentration ability, primarily through its association with reading and listening focus (RLF) and control of focus before sleep (CFBS) (16).

Concentration ability based on Krawietz Concentration Scale (KCS) is found to be positively correlated with the Mindfulness Questionnaire (MQ), Boredom Proneness Scale (BPS), and The Adult Behavior Checklist (ABC) (17). Mindfulness training on sensory stimulation such as breath movements can reduce bronchial asthma symptoms subjectively and positively correlate with the ability to concentrate (17,18). The BPS value is positively correlated with somatization in the Hopkins Symptom Checklist (HSCL), which included complaints of difficulty breathing (19,20).

To date, not many studies have analyzed the relationship between the overall history of respiratory allergies and concentration ability in young adults. This study aims to prove the relationship between respiratory allergy and concentration ability in young adults.

METHODS

Design

The research design is a retrospective study with a cross-sectional observational type. The research was conducted at the Faculty of Medicine, Universitas Nahdlatul Ulama Surabaya, Surabaya, Indonesia.

Sample

The population of this study was young adults. The population must meet the inclusion and exclusion criteria. The inclusion criteria included all students aged 18-25 years with or without respiratory allergies. In comparison, the exclusion criteria included a history of smoking in the last two years, a history of lung disease and intra-abdominal masses based on the doctor's verdict, and an average sleep duration of fewer than 5 hours in the past month.

Sampling was done by the total sampling technique and cluster random sampling. The sample size that must be met to identify the prevalence of respiratory allergy was 133 people who met the minimum requirements (n1=100). The sample size to analyze the relationship between respiratory allergy and some/all components of concentration ability was 16 people per group (including sleep duration criteria), which also met the minimum requirements (n2=15).

Measurement

Respiratory allergies were assessed based on the subject's history which met the criteria for measuring respiratory allergies during the past year. Criteria ≥3 of 9 were for prevalence, and criteria ≥1 of 9 were for different tests. The Respiratory Allergy Prediction test (RAPt) questionnaire was used to collect respiratory allergy data. The results obtained were subjects with positive RAPt and negative RAPt. Meanwhile, concentration ability is an assessment of a subject's concentration based on measuring instruments which include control of focus (CF), uncontrolled focus (UF), RLF, and/or CFBS. The KCS questionnaire was used to collect concentration ability data with a score of 49-343. The RLF component shows a person's ability to maintain attention in visual (reading) and auditory (listening) stimuli. The CFBS component showed a person's ability to ignore all internal and external stimuli to fall asleep. The CF and UF components are non-specific in showing the ability to maintaining attention to stimuli and control motor (writing) and verbal (speaking) responses. Thus, RLF and CFBS were components of concentration ability that were more relevant to the inner-outer psychoneurological process.

Data Collection

Data collection was carried out on a primary basis. Subjects with RAPt measurement results that met at least 3 of the 9 criteria were included in the RAPt (+) group, while KCS was presented in the form of scores with a range of 49-343. The characteristics of the subjects observed were age, gender, the proportion of respiratory allergies with criteria RAPt ≥3 and RAPt ≥1, and KCS and its components. The data were displayed in the form of mean and standard deviation (SD).

Data Analysis

Univariate analysis was performed using the data normality test (Kolmogorov-Smirnov) on KCS score. The score was presented in mean forms and 95 % confidence interval (CI) if normally distributed. Other alternatives were presented in terms of median and minimum-maximum values. All data were presented in tabular form. Bivariate analysis was performed by unpaired t-test on mean KCS score if normally distributed. Another alternative will be tested with the Mann-Whitney test. The value of $\alpha = 0.05$ was used as a limit in determining the accepted hypothesis. Data analysis was carried out using free licensed software, namely the Statistical Analysis System (SAS) University Edition.

RESULTS

In total, 149 study subjects met the inclusion and exclusion criteria, as shown in Table 1. The average age of the study subjects was 19.30 ± 0.96 years, with the highest proportion of sex being female, which was 67.79 %. The proportion of respiratory allergies with RAPt 3 criteria was 4.70 %, while those with RAPt 1 were 42.95 %. The KCS value of the research subjects was 194 ± 14 with a CF value of 64 ± 11, UF 67 ± 12, RLF 39 ± 5, CFBS 23 ± 4, and RLF-CFBS 62 ± 7.

Table 1.

Characteristics of research subjects

Characteristics (n=149)	Mean ± SD or Proportion
Age (years)	19.30 ± 0.96
Sex	
Male	48 (32.21 %)
Female	101 (67.79 %)
Respiratory allergy with RAPt > 3	
RAPt3+	7 (4.70 %)
RAPt3-	142 (95.30 %)
Respiratory allergy with RAPt ≥ 1	
RAPt1+	64 (42.95 %)
RAPt1-	85 (57.05 %)
Krawietz Concentration Scale (KCS)	194 ± 14
Control of Focus (CF)	64 ± 11
Uncontrolled Focus (UF)	67 ± 12
Reading and Listening Focus (RLF)	39 ± 5
CF Before Sleep (CFBS)	23 ± 4
RLF-CFBS	62 ± 7

RAPt: Respiratory Allergy Prediction test

The prevalence of respiratory allergy in young adults in 2017 was 4.7 % (n= 149). Results of analysis showed that there was no relationship between respiratory allergy and RLF (p= 0.231), CFBS (p= 0.544), and the combination of RLF-CFBS (p= 0.524). Overall, there was no association between respiratory allergy (RAPt > 1) and KCS (p= 0.538). In addition, there was a

significant tendency association (p=0.070) with a 90 % confidence level between respiratory allergy and UF. In contrast, the analysis results showed an association between respiratory allergy (RAPt ≥3) and KCS (p= 0.029).

DISCUSSION

The results showed no association between respiratory allergy (RAPt 1) with RLF, CFBS, RLF-CFBS combination, and concentration ability. However, there was an association between respiratory allergy (RAPt ≥1) and UF, and there was an association between respiratory allergy (RAPt ≥3) and concentration ability. Respiratory allergies tend to decrease concentration ability through mechanisms that do not involve a decrease in sleep quality or reaction time. Decreasing concentration ability in patients is caused by an increased cholinergic response to acetylcholine and decreased beta-adrenergic response to norepinephrine (12). This condition decreases the activity of the reticular-activating system (RAS) in the brain (15), which is associated with decreasing concentration ability through other mechanisms that do not involve sleep quality and reaction time. However, this needs to be investigated further.

Decreased concentration ability is also significantly associated with a respiratory allergy when using the RAPt ≥3 criteria. Decreased concentration ability can elevate respiratory allergy manifestation through the HPA axis pathway (18). This HPA axis correlation is caused by a decrease in mindfulness, which is directly lower concentration ability proportionally (17). However, this needs to be proven in research that using mindfulness indicators.

Previous studies have shown the role of RAS in concentration ability, which is a relationship between reaction time and concentration ability, especially in RLF and CFBS components. CFBS's role is also supported by a negative correlation between sleep patterns (Pittsburgh Sleep Quality Index) and reaction time. Respiratory allergies are related to concentration ability through RAS activity, especially in maintaining an awake state and sleep. Studies show CBFS components are directly related to sleep patterns (16). CBFS affects sleep quality deterioration in terms of the ability to initiate sleep so that RAS activity is decreased.

The opposite correlation between concentration ability and respiratory allergy appears as a correlation of KCS (concentration ability) with MQ (mindfulness) along with BPS and ABC (17). Increased mindfulness can reduce the frequency of asthma symptoms by decreasing the stress response and increasing the hypothalamus-pituitary-adrenal (HPA) axis to secrete cortisol (18).

Respiratory allergy assessment such as skin prick test (SPT), in vitro IgE examination, allergen provocation, and other molecular tests are needed to determine whether referral for further allergy testing is necessary. This examination requires a high cost and is not generally available so that an inexpensive examination can be developed that can be carried out by general practitioners. The RAPt questionnaire is considered adequate because it is easy to use in clinical practice and has a relatively affordable price. This questionnaire contains nine questions related to respiratory allergies, which include both allergic rhinitis and asthma (1).

The ability to concentrate as a cognitive process refers to attention. There are three correlation variations between concentration ability and focused attention: 1) concentration as part of the attention process; 2) concentration as a distinct process of attention; or 3) concentration as a combination of two or more types of attention. Some researchers use the first variation, which considers concentration level as one of several types of attention, namely focused attention, sustained attention, controlled attention, and vigilance. Thus concentration ability is the ability to maintain attention and reduce distraction beyond self-control despite thought stimuli or internal or external stimuli. The distraction itself must not lose awareness of the previous object of attention (17).

A decrease in only concentration ability cannot be considered as a disorder or disease because there were variations in a person's concentration ability, especially in school-age children. There are three main methods for assessing concentration ability: performance-based concentration checks, structured interviews,

and self-assessment scales. Among the three, the self-assessment scale is the most practical examination method and can be used to measure the degree of concentration ability in subclinical conditions quantitatively (21)

The method of examining concentration ability with the Krawietz Concentration Scale is a method with a self-assessment scale. This method was developed because the previous methods were too specific for particular needs, such as concentrating on sports. The test of Attentional and Interpersonal Style (TAIS) concentration ability assessment method is considered unable to measure all components of concentration ability and has low reliability. This concentration scale has shown good reliability, with a Cronbach alpha value of 0.93 (17).

CONCLUSION

The results of this study showed a significant relationship between respiratory allergy (RAPt ≥3) and the ability to concentrate, although there was no significant relationship between respiratory allergy (RAPt ≥1) with UF, RLF, CFBS, RLF-CFBS combination, and concentration ability. Patients with respiratory allergies should pay attention to the RAPt score in choosing the type of work.

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Mental health, depression, and quality of life levels in heart failure patients

Niveles de salud mental, depresión y calidad de vida en pacientes con insuficiencia cardíaca

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SUMMARY

Introduction: *Heart failure is the most common cause of death. About 20 %-40 % of heart failure patients' have depressive disorders. Improvements in patients' quality of life could give an effect on the progression of cardiovascular disease. This study aims to describe depression and quality of life in heart failure patients.*
Methods: *This study was conducted using the Beck Depression Inventory (BDI) questionnaire and the Short-form 36 (SF36) questionnaire in heart failure patients' populations during January-March 2020.*
Results: *65 subjects were obtained in this study. Consisted of 37 male subjects (57 %), 28 female subjects (43 %). The highest ages were 61-70 years (38.5 %) and 51-60 years (36.9 %). Thirty-eight respondents (38.58 %) had no symptoms of depression. The mental health dimension has the highest score, with 76,123 median values. At the same time, the dimension of functional limitations related to emotional problems has the lowest score, with a 56,410-median value. There were 22 subjects (22.34 %) with mild depressive symptoms, 5 subjects (5.8 %) with moderate depressive symptoms, whilst none of the populations had severe depressive symptoms.*
Conclusion: *The most common depiction of depression in heart failure patients is no symptoms of depression, mild depression, and moderate depression. The best depiction of the quality of life in heart failure patients is the mental health dimension, and the lowest is function limitation related to emotional problems.*

Keywords: *Heart failure, depression, quality of life.*

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RESUMEN

Introducción: *La insuficiencia cardíaca es la causa más común de muerte. Aproximadamente entre el 20 % y el 40 % de los pacientes con insuficiencia cardíaca tienen trastornos depresivos. Las mejoras en la calidad de vida de los pacientes podrían influir en la progresión de la enfermedad cardiovascular. Este estudio tiene como objetivo describir la depresión y la calidad de vida en pacientes con insuficiencia cardíaca.*
Métodos: *Este estudio se realizó utilizando el cuestionario Beck Depression Inventory (BDI) y el cuestionario Short-form 36 (SF36) en poblaciones de*

pacientes con insuficiencia cardíaca durante enero-marzo de 2020.
Resultados: *En este estudio participaron 65 sujetos. Consistió en 37 sujetos masculinos (57 %), 28 sujetos femeninos (43 %). Las edades más altas fueron 61-70 años (38,5 %) y 51-60 años (36,9 %). Treinta y ocho encuestados (38,58 %) no tenían síntomas de depresión. La dimensión de salud mental tiene la puntuación más alta, con 76 123 valores de mediana. Al mismo tiempo, la dimensión de limitaciones funcionales relacionadas con problemas emocionales tiene la puntuación más baja, con un valor mediano de 56.410. Hubo 22 sujetos (22,34 %) con síntomas depresivos leves, 5 sujetos (5,8 %) con síntomas depresivos moderados, mientras que ninguna de las poblaciones presentó síntomas depresivos graves.*
Conclusión: *La descripción más común de depresión en pacientes con insuficiencia cardíaca es la ausencia de síntomas de depresión, depresión leve y depresión moderada. La mejor descripción de la calidad de vida en pacientes con insuficiencia cardíaca es la dimensión de salud mental, y la más baja es la limitación funcional relacionada con problemas emocionales.*

Palabras clave: *Insuficiencia cardíaca, depresión, calidad de vida.*

INTRODUCTION

Cardiovascular disease is a non-communicable disease that contributes to the high mortality rate in the world. The death rate for cardiovascular disease in the world in 2008 reached 17 million. This rate is expected to rise from year to year until it reaches 25 million deaths by 2030 (1). Demographic changes that occur with epidemiological and nutritional transitions is a key role in cardiovascular disease shifting from developed to developing countries as a burden disease. In Indonesia, cardiovascular disease is the leading cause of morbidity and mortality and is responsible for one-third of all causes of death in Indonesia (2). The incidence of heart failure is still difficult to determine because there are only a few data available, especially in developing countries, but it is estimated that around 23 million people suffer from heart failure worldwide (3). Meanwhile, the overall incidence of coronary disease in Indonesia reached 138 380 or 9.89 % of the total deaths. Data shows that coronary disease ranks seventh highest in non-communicable diseases in Indonesia (4).

Chronic heart failure is defined as a pathological condition in which the heart cannot pump blood flow throughout the body so that metabolic body tissues requirement was not fulfilled. Heart failure can also be interpreted as a clinical syndrome, which consists of symptoms of dyspnea, fatigue (during activity and rest), accompanied by fluid retention symptoms such as edema in the ankles and lung congestion (5). Heart failure causes according to national heart failure surveys, are dominated by hypertension (53 %), ischemic heart disease (47 %), diabetes (28 %), and valvular heart disease (21 %) (6). Pathophysiology of heart failure requires an initial understanding of the typical clinical syndromes, circulatory disorders, structural abnormalities of the heart, hemodynamic and fluid balance disorders, biochemical abnormalities (reduced energy, decreased contractility), neurohumoral activity that causes maladaptive cardiac hypertrophy, and genetic involvement in heart failure (7,8).

Depression is a common comorbid condition among heart failure patients. Prevalence of depression ranges from 23.8 % to 67 % in inpatients and about 16.7 % to 70 % in outpatients with heart failure (9). There is a two-way relationship between heart failure and depression. Sometimes heart failure leads to the development of depression, and sometimes the same pathophysiological mechanisms leading to clinical manifestations of both conditions (10). 20 % to 40 % of patients with heart failure meet the criteria for major depressive disorder or experience an increase in depressive symptoms. This figure far exceeds the prevalence of 2 %-9 % seen in the normal population (11,12). Depression is a major cause of functional disability due to the patient's inability to cope with everyday stressors. Depression can be caused by many factors, including heredity and genetics, constitution, premorbid personality, physical, psychobiological, and neurological factors, biochemical factors, and electrolyte problems (13).

Research shows that depression is the strongest predictor of health status and quality of life in patients with heart failure (9). Depressed patients show decreased function in daily activities, increased heart failure symptoms intensity, and impaired quality of life. Other studies have

shown that heart failure patients with depression have a high risk for re-hospitalization and death compared with heart failure patients who are not depressed (11,12,14). Heart failure patients with depression have the highest risk for non-adherence in treatment, leading to decreased health status (9).

Quality of life (QoL) is a satisfactory level of life. QoL, according to WHO, is the perception of individuals about their position in life in the context of the culture and value system in which they live concerning their goals, hopes, and interests (15,16). Improvement and recovery of QoL is an important aspect in managing cardiovascular disease with depression so that it affects the quality of life, which can predict the further development of cardiovascular disease (17). Evaluation of health-related quality of life (HRQoL) is described as a treatment measurement for potential patient life changes. Several studies have also shown that several factors such as comorbid disease, depression, anxiety, and the incidence rate of invasive cardiovascular procedures are associated with increased HRQoL in patients with cardiovascular disease (18).

Seeing the phenomenon of many heart failure patients who suffer from depression can interfere with the quality of life, and there is no previous research has been conducted at the Jemursari Islamic Hospital Surabaya, which makes authors conduct this study. This study aims to determine the description of depression and the quality of life of heart failure patients.

METHODS

This study is a cross-sectional descriptive study of heart failure patients at the Cardiac and Vascular Outpatient Installation at Jemursari Islamic Hospital, Surabaya, Indonesia. The study was conducted from January to March 2020. The inclusion criteria in this study were: all heart failure patients at the Cardiac and Vascular Outpatient Installation at Jemursari Islamic Hospital, Surabaya in January – March 2020 who were willing to become respondents and answer the Beck Depression Inventory (BDI) questionnaire and the Short-form questionnaire 36 (SF36). Exclusion criteria included patients with psychotic conditions. The data sources of this study were heart failure patients' data at the Cardiac and Vascular Outpatient installation at Jemursari Islamic Hospital Surabaya, BDI questionnaire, and SF36 questionnaire. Data were collected and processed by descriptive statistical methods in the form of tables and then presented in diagrams. Table 1 shows the operational definition of variables.

This study used the variables of heart failure, depression, and quality of life. Heart failure by definition is a clinical syndrome characterized by characteristic symptoms: shortness of breath, ankle swelling, fatigue, and increased jugular venous pressure, pulmonary crackles, and peripheral edema caused by structural or functional cardiac abnormalities. This results in reduced cardiac output and high intracardiac pressure both at rest and at the activity. The condition of heart failure is measured based on anamnesis and physical examination by a cardiologist.

Depression is defined as a syndrome characterized by several clinical symptoms that manifest in each individual differently. Depression syndrome can be affective, somatic, motivational, cognitive. This variable is measured using the BDI II (ordinal) scale, with a range of 0-63. Score 0-9 is considered as no symptoms of depression, score 10-18 is considered as mild depression symptom, score 19-29 is considered as moderate depression symptom, and score 30-63 is considered as major depression symptom.

Quality of life is an individual's perception of their position in life in the context of the culture and value system in which they live in terms of goals, expectations, and interests. Quality of life was measured using the SF-36, which has a score range of 0-800. The final score was determined based on the total score for the dimensions of physical function, functional limitations related to physical problems, functional limitations related to emotional problems, energy/fatigue, mental health, social functioning, pain, general health perception, then the mean and standard deviation (numeric) values were searched.

RESULTS

Demographic Characteristics of Heart Failure Patients at the Cardiac and Vascular Inpatient Installation, Jemursari Islamic Hospital, Surabaya

Table 1 shows the demographic characteristics of patients in this study. The total number of respondents was 65 people with more males than females (57 %). The highest ages were in the range of 61-70 years (38.5 %) and 51-60 years (36.9 %). Some fewer respondents were unemployed (40 %). The most subject was high school graduated (37 %). 36 respondents (56 %) had lower middle income, with a total income less than IDR 2 500 000.00. 45 respondents (69.2 %) suffered from heart failure for more than two years. 50 respondents (77 %) had undergone treatment for more than one year (77 %). 45 % of respondents feel support from family, while 39 respondents (60 %) had sufficient support from relatives, friends, and medical personnel. 56 respondents (86 %) interpreted heart failure as a test or life's problems.

Table 1

Demographic Characteristics of Heart Failure Patients at the Cardiac and Vascular Outpatient Installation of Jemursari Islamic Hospital, Surabaya

No.	Characteristics		Frequency (n=65)	Percentage (%)
1	Sex	male	37	57.0
		female	28	43.0
2	Age	≤ 40 years	3	4.6
		41 – 50 years	4	6.2
		51 – 60 years	24	36.9
		61- 70 years	25	38.5
		71- 80 years	9	13.8
3	Occupation	government employees	3	13.8
		Private employees	8	4.7
		Entrepreneur	14	12.3
		Not working	26	21.5
		Others	14	40.0
4	Education Level	Elementary School	17	26.0
		Junior High School	12	19.0
		Senior High School	24	37.0
		College	12	18.0
5	Monthly income (IDR)	< 2 500 000	36	56.0
		2 500 000 – 4 999 000	21	32.0
		5 000 000 – 10 000 000	6	9.0
		> 10 000 000	2	3.0
6	Period of heart failure suffering	6 months – 1 year	10	15.4
		1 – 2 years	10	15.4
		> 2 years	45	69.2
7	Period of treatment	< 6 months	8	12.0
		6 months – 1 year	7	11.0
		> 1 year	50	77.0
8	Family support	Very sufficient	29	45.0
		Sufficient	34	52.0
		Insufficient	2	3.0
9	Support outside the family	Very sufficient	15	23.0
		Sufficient	39	60.0
		Insufficient	7	10.7
		Very sufficient	4	6.0
10	The meaning of being sick	Life’s problems/tests	56	86.0
		Punishment	2	3.0
		Warning	7	11.0

Overview of Depression and Quality of Life of Heart Failure Patients at the Cardiac and Vascular Outpatient Installation, Jemursari Islamic Hospital, Surabaya

In Table 2, there are 38 respondents with no symptoms of depression (38.58 %), 22 respondents with mild depressive symptoms (22.34 %), five people with moderate depression symptoms (5.8 %), and no respondents who experienced symptoms of major depression.

Table 2

Overview of depression in heart failure patients

No	Characteristics	Frequency (n=65)	Percentage (%)
1	No symptoms of depression	38	58.4
2	Mild depression symptoms	22	33.8
3	Moderate depression symptoms	5	7.0
4	Major depression symptoms	0	0.0

Overview of the Quality of Life of Patients with Heart Failure at the Cardiac and Vascular Outpatient Installation, Jemursari Islamic Hospital, Surabaya

Table 3

Overview of the quality of life of patients with heart failure at the cardiac and vascular outpatient installation, Jemursari Islamic Hospital, Surabaya

No	Dimensions of Quality of Life	0 - 100	N	Mean	SD
1	Physical function	0 - 100	65	70.923	28.393
2	Functional limitations related to physical problems	0 - 100	65	58.462	45.560
3	Pain	0 - 100	65	68.731	25.067
4	General health	0 - 100	65	58.333	18.837
5	Energy/tired	0 - 100	65	67.692	18.330
6	Social function	0 - 100	65	58.654	15.456
7	Functional limitations related to emotional problems	0 - 100	65	56.410	47.479
8	Mental health	0 - 100	65	76.123	14.106
Total Quality of Life Score		0 - 800	65	515.328	213.228

DISCUSSION

In this study, the depiction of depression in most heart failure patients was that there were no depressive symptoms. The best description for quality of life in heart failure patients is t mental health dimension, and the lowest is the functional limitations related to emotional problems. Most respondents in this study had no symptoms of depression. This is different from other studies, which state that many patients with heart failure suffer from depression (11,19). This various result is due to male subjects is frequent than females, while the prevalence of depression in heart failure patients is more frequent in females

than males (20). In this study, there were more males than females. This is in concordance with data from the American College of Cardiology Foundation/American Heart Association, which shows that the prevalence of heart failure in black and white men is more than in women's (14), whereas women have a lower risk for heart failure than men (21). Besides that, the meaning of pain perceived by respondents will affect emotional stress, such as symptoms of depression (22). The meaning of pain in most respondents is as a trial; only a few perceive pain as a punishment. Patients with negative perceptions about heart disease are prone to depression (22).

This study indicates that family and non-family support is very sufficient and sufficient for respondents. This shows that good support will prevent respondents from stressful conditions, increase adherence to medication and a healthy lifestyle. Other studies suggest that lack of social support can increase the incidence of hospitalization and the risk of death (14). Besides family and non-family support, there are studies shows that environmental factors, including sociodemography, can influence the onset of depression in patients with physical disorders, including age, gender, marital status, education, social support, and a history of depression or physical disturbance (23). The treatment duration will also affect mood conditions (24).

The mental health dimension has the highest value in this study, this result is in line with previous studies (25). In this study, the majority of respondents underwent treatment for more than one year. This indicates that the doctor-patient relationship is well established. Previous studies have shown that an effective doctor-patient relationship helps regulate patient emotions and facilitates understanding of information, ultimately leading to patient satisfaction and a better quality of life (26). In this study, it was also found that family and non-family support were quite good to improve the quality of life of heart failure patients. This result is also in concordance with previous research (25) In this study, many respondents did not have depressive symptoms, so the quality of life in this study is considered as good. Because depressive symptoms will affect the quality of life (24,27).

Another dimension of quality of life is the mental health dimension. This study's lowest quality of life dimension was the dimension of functional limitations related to emotional problems. This is consistent with a study that investigated the impact of chronic disease on quality of life among elderly whose living in various parts of the state of São Paulo, Brazil, where depression/anxiety was the most negative impact on vitality, emotional roles, social functioning, and mental health (28). Other studies have shown that patients who felt their illness had a more significant effect, and their emotional quality was less qualified (24).

Characteristics of respondents were described demographic conditions of respondents and used to assess some factors that influence depression and QoL in research respondents. In terms of age, the highest percentage is in the range of 61-70 years. This is following data from the AHA statistical update, which states that heart failure approaches 21 per 1 000 population after the age of 65 years. There is an increase among the elderly (29,30), and it is estimated that Japanese people 65 years of age had higher numbers of heart failure incidence (31). The high prevalence and incidence of heart failure among the elderly may be related to heart failure risk factors that increase with age, such as coronary artery disease and hypertension, and age-related maladaptive changes that can directly affect the cardiovascular system (30). Most of the research subjects did not work, with the most education of senior high school and low family economic income, which was less than IDR 2 500 000.00. Cohort research conducted on black and white populations in the southeastern United States showed an independent relationship between socioeconomic characteristics (income, education, and occupation) and the risk of heart failures (32).

Many respondents suffered from heart failure for more than two years in this study. The duration of illness makes patients easily adapt to chronic diseases, such as heart failure. Patients will strive to understand and manage their problems (24). Most respondents underwent treatment after one year, worries less about treatment because they were used to it, and felt most benefits from the treatment they had (24).

CONCLUSION

The most common description of depression in heart failure patients is that there are no symptoms of depression, mild depression, and moderate depression. The best description of the quality of life of heart failure patients is the mental health dimension, and the lowest in the functional limitation related to emotional problems. Further research needs to be done with a more straightforward questionnaire and biological markers in future studies to determine the description of depression in heart failure patients.

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Profile of unnatural mortality at tertiary hospital

Perfil de mortalidad no natural en un hospital terciario

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SUMMARY

Introduction: *Unnatural deaths are deaths that can be prevented, the frequency of which reflects the quality of public health services. Unnatural deaths occur due to external causes such as suicide, homicide, and accidents. This study aims to analyze the profile of cases of unnatural death at Dr. Soetomo General Hospital, Surabaya, Indonesia.*
Methods: *This research was a descriptive-analytic study with a cross-sectional study approach. The secondary data was collected using an autopsy profile instrument from the medical record for unnatural death cases.*
Results: *The results showed that out of 2 277 corpses from January 2014 to December 2016, 70 corpses were cases of unnatural death. Most corpses who experience unnatural deaths were male (62.9 %). The highest number of unnatural deaths occurred due to homicide (54.3 %). The most cause of unnatural death was blunt violence (48.6 %). The most mechanism of unnatural death occurred by asphyxia (71.4 %). Meanwhile, most corpses were injured in the front of the neck, chest, and abdomen (40 %). There was a significant relationship between the type of injury and unnatural death (p = 0.001), however, no relationship was found between wound region and unnatural death (p= 0.217). There were significant differences between the type of injury in unnatural death cases (p= 0.037).*
Conclusion: *There was a relationship and differences in the types of corpse injuries with unnatural deaths.*

Keywords: *Unnatural death, injury, autopsy*

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RESUMEN

Introducción: *Las muertes no naturales son aquellas que se pueden prevenir y cuya frecuencia refleja la calidad de los servicios de salud pública. Las muertes no naturales ocurren por causas externas como suicidio, homicidio y accidentes. Este estudio tiene como objetivo analizar el perfil de casos de muerte no natural en el Hospital General Dr. Soetomo, Surabaya, Indonesia. Métodos: esta investigación fue un estudio descriptivo-analítico con enfoque de estudio transversal. Los datos secundarios se recopilaron utilizando un instrumento de perfil de autopsia del registro médico para casos de muerte no natural.*
Resultados: *Los resultados mostraron que de los 2 277 cadáveres de enero de 2014 a diciembre de 2016, 70*

fueron casos de muerte no natural. La mayoría de los cadáveres que experimentaron muertes no naturales eran hombres (62,9 %). El mayor número de muertes no naturales ocurrió por homicidio (54,3 %). La mayor causa de muerte no natural fue la violencia contundente (48,6 %). El mayor mecanismo de muerte no natural ocurrió por asfixia (71,4 %). Mientras que en los cadáveres la zona que resultó mayormente con heridas fue la region frontal del cuello, pecho y abdomen (40 %). Hubo relación estadísticamente significativanentre el tipo de lesión y la muerte no natural (p= 0,001), sin embargo, no se encontró relación entre la región de la herida y la muerte no natural (p= 0,217). Hubo diferencias significativas en el tipo de lesión en los casos de muerte no natural (p= 0,037).

Conclusión: *Hubo una relación y diferencias en los tipos de lesiones de cadáveres con muertes no naturales.*

Palabras clave: *Muerte antinatural, lesión, autopsia.*

INTRODUCTION

Every year, about 800 000 people die due to suicide. In other words, every 40 people deliberately kill themselves so that the number of deaths due to suicide increases more than deaths due to homicide (1). Each year, the suicide rate is increasing all over the world. The global annual mortality rate has been estimated by the World Health Organization (WHO) to be 10.7 per 100 000 people, with variations across age groups and countries (2). The Birth and Death Registration Act No. 51 of 1992 requires doctors to issue a death certificate and a death notification form stating the cause of death, which may be natural or unnatural (3).

The contribution of specific causes of death to excess mortality has not been widely studied because of the difficulty of reaching this vulnerable population. Numerous studies in several countries have shown an increasing proportion of deaths from substance abuse, accidents, suicide and homicides, mental disorders, infectious diseases, and ischemic heart disease (4-6). In comparison, natural death occurs through disease progression, and unnatural deaths occur due to external or morbid causes, including suicide, homicide, and accidents. The cause of unnatural death is because most of the homicides are asphyxia accompanied by blunt force violence and mainly occur in child homicide (7).

Unnatural death is the leading cause of death in the homeless cohort in Rotterdam. As many as 26 % of morbid deaths are a much greater cause of death in homeless people than in the general Rotterdam population (4 %). Compared to the general population of the city, the homeless in Rotterdam have a 15 times higher risk of dying from unnatural causes. Half of all unnatural deaths in this group are due to intentional injuries, such as suicide and homicide (4,5). A study comparing mortality ratios and estimated years of death in two cohorts — opioid-dependent subjects from the United States (US) and Taiwan — showed that half the subjects died of morbid causes in both cohorts, with overdose being the most common cause of death in the US, cohort (US: 80.6 %, Taiwan: 25 %) compared to suicides in the Taiwan cohort (Taiwan: 51.9 %, US: 2.8 %) (8). In Singapore, 51.07 % of the cases between 2009 and 2010 reported were unnatural deaths that included drug toxicity/ adverse reactions (6.93 %). Drops from height (35.86 %), accidents (17.6 %), and drowning (5 %) were also reported. However, the number of drug users among cases was unknown (8).

A retrospective study of tourist deaths over 46 years at Lake Powell in the US reveals that 73 % of deaths at this popular reservoir were due to accidental injury (9). Drowning was the second leading cause of accidental death among American travelers abroad in 1975 and 1984, accounting for 16 % of all travel deaths. It was also the cause of death for 9 % of Peace Corps Volunteers during their service period between January 1984 and December 2003 (9). This study aims to analyze the autopsy profile of cases of unnatural death.

METHODS

This was a descriptive-analytic study with a cross-sectional approach, namely an epidemiological research design that studies the prevalence, distribution, and the relationship between disease and exposure (research factors) by observing the disease exposure status or characteristics. The research was carried out at the Forensic and Medicolegal Medical Installation of Dr. Soetomo Hospital, Surabaya, Indonesia, from January 2014 to December 2016. The

population of the study was all corpses in the Forensic Medicine and Medicolegal Installation of Dr. Soetomo Hospital, Surabaya, Indonesia. The sample in this study were corpses with cases of unnatural death, which were taken using simple random sampling. The data in this study were secondary data collected by using an autopsy profile instrument for abnormal death cases by observing medical record data. The data were analyzed using the Chi-square test. The degree of confidence used is 95 %. A value of $p<0.05$ was considered as a significant relationship between the two variables studied.

RESULTS

From January 2014 to 2016, the number of deaths recorded was 2 277, with a total number of natural deaths of 72 and unnatural deaths of 70. Table 1 shows that most corpses who experience unnatural deaths were males (62.9 %). Of the total 70 unnatural deaths, 17 corpses (24.3 %) were aged 36-45 years. The lowest incidence of unnatural death occurred at ages 5-11 and ages 12-16 years. The highest cause of death was blunt violence (48.6 %).

Most of the mechanisms of unnatural death occurred with asphyxia (71.4 %). The number of wounds on the corpse with an unnatural death was at most ≤ 3 (68.6 %) and the type of injury that often occurred was fracture (24.3 %). Meanwhile, the majority region indicated the corpses were injured in the front of the neck and chest, abdomen (40 %). The majority of unnatural deaths occurred due to homicide (54.3 %).

Based on the results of the Chi-square test, there was a significant relationship between the type of injury on the corpse and the unnatural death ($p=0.001$). However, there was no relationship between the wound region and the unnatural death ($p=0.217$).

There was a difference between types of injuries and cases of unnatural death on the corpse ($p<0.037$). However, the difference between the wound region of the corpse and the case of unnatural death showed no statistical difference ($p=0.843$).

Table 1

Frequency distribution of corpses at unreasonable deaths

Characteristics		Frequency	Percentage
Sex	Male	44	62.9
	Female	26	37.1
Age	0 - 5 years	8	11.4
	5 - 11 years	1	1.4
	12 - 16 years	1	1.4
	17-25 years	10	14.3
	26 - 35 years	8	11.4
	36 - 45 years	17	24.3
	46 - 55 years	11	15.7
	56 - 65 years	8	11.4
	> 65 years	6	8.6
Cause of death	Sharp Violence	16	22.9
	Blunt Violence	34	48.6
	Chemistry	2	2.9
	Electricity	2	2.9
	Entry of Water	13	18.6
	Poison	3	4.3
Death mechanism	Asphyxia	50	71.4
	Bleeding	20	28.6
Number of wounds	≤ 3	48	68.6
	> 3	22	31.4
Types of injury	Fracture	17	24.3
	Laceration	3	4.3
	No Abnormalities	9	12.9
	Torn	3	4.3
	Blisters Pressed	3	4.3
	Valid Bruises	16	22.9
	Punctured	12	17.1
	Sliced	1	1.4
	Burn it	4	5.7
	Blisters	2	2.9
Region of wounds	Head, Back Neck, Back, Upper Limbs, Hands	25	35.7
	Front Neck, Chest, Abdominal	28	40.0
	Forearm	3	4.3
	Combinations of 2 & 3	3	4.3
	Combinations 1 & 2	11	15.7
Death	Murder	38	54.3
	Suicide	3	4.3
	Accident	29	41.4

DISCUSSION

The average autopsy performed at the Forensic Medicine and Medicolegal Installation of Dr.

Soetomo General Hospital, Surabaya, Indonesia, experienced a downward trend during the period January 2014 to December 2016. Statistically, it shows a relationship between the type of injury and the unnatural death (homicide, suicide, accident), and there is a significant difference between the types of injuries in homicide, suicide, and accident cases. Statistically, it also shows no relationship between the wound area and morbid mortality, and there is no difference between the regions in homicide, suicide, or accident cases.

The types of stab wounds and bruises are primarily found in homicides than in suicides and accidents. Perpetrators of murder cases often use sharp weapons, such as knives. Meanwhile, bruises are often found as resistance wounds from the victim to the perpetrator and cases of murder by maltreatment. Blunt force trauma also causes fractures resulting in internal or external bleeding (10). Types of fracture wounds (fractures) are most often found in accident cases than in cases of homicide or suicide. Fractures in accidents are often found in cases of falls from a height or traffic accidents and work accidents, types of fractures that are fatal, especially head fractures, and often occur in men of productive age (11).

The wound region is also one of the parameters used to determine the mode of death. Suicide perpetrators find it challenging to reach the back region of the corpse (back, back neck). The most common injuries to the head region were those who committed suicide with a firearm rather than a sharp weapon. The hand and upper arm regions are the regions that occur most frequently in cases of murder as a form of resistance injury. Meanwhile, the forearm is the region most frequently used by suicides as a form of trial injury. The front region of the neck, chest, and abdomen are the most challenging regions to estimate the mode of death. However, other research states that the neck region is the main target of murder because it is easily reached by hand (12).

The sex distribution of the corpses was 62.9 % male and 37.1 % female, the same result as other studies, which state that male corpses experienced more unnatural deaths than women (13). Men are more dominant victims of homicide/suicide/accident because men interact more with the environment outside the home, both socio-economically as workers, while women mostly stay indoors. Men have a higher risk of experiencing sudden death than women, and the incidence rate will increase with age (14).

The age distribution of the corpses shows that most of the victims are in the age range of 36 - 45 years. Several studies have also stated that the age of corpses who die unnaturally occurs mainly at productive age (1). This age range is the productive age for work, so that they interact a lot with the environment and other people, especially in big cities, for example, Surabaya, which is a destination city to find a job or a more decent living from the surrounding areas.

The cause of most deaths in cases of unnatural death obtained from this study's results is blunt violence. The cause of death is unnatural because most homicides are asphyxia accompanied by violence with blunt objects (7). Intense violence also occurs more in cases of homicide than in suicide. This statement is the same as the results obtained in this study because the tool that is often used in homicide cases is a sharp weapon to produce deadly wounds.

The most common mechanism of death is asphyxia. The mechanism of asphyxia death occurs more in accidents and suicides than in homicides (12). The mechanism of death asphyxia in accident cases often occurs due to skull fracture or drowning. Meanwhile, in cases of suicide occur due to hanging (1).

The number of wounds is divided into two: the number of wounds less and equal to 3 and the number of wounds more than three. The assumption is that a higher number of wounds is associated with a higher likelihood of homicide. A large number of wounds (more than 3) is found more in cases of homicides and accidents than in cases of suicide. In the homicide case, the victim's resistance against the perpetrator is found. For example, wounds in the upper limb area are also an essential parameter for investigators and doctors in examining cases of suspected murder. Whereas in the case of accidents, a large number of injuries can be found in all parts of the body accompanied by several types of injuries at once (15).

CONCLUSION

Unnatural deaths in Dr. Soetomo Hospital, Surabaya, Indonesia, showed as many as 70 corpses with cases of homicide, suicide, and accidents. This study proves a relationship and differences in the types of corpse injuries with morbid deaths based on an autopsy at the Forensic Medicine and Medicolegal Installation of Dr. Soetomo Hospital, Surabaya, Indonesia, for the period January 2014 - December 2016. This study also concluded that there was no relationship and difference between the regions of corpse wounds and unnatural deaths based on autopsy.

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Conflicts of Interest

The authors have no conflict of interest to declare.

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Characteristics of reproductive-aged women with unmet need for family planning

Características de mujeres en edad reproductiva con necesidad insuficiente de planificación familiar

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SUMMARY

Introduction: *One factor that led to the increase in population was the unfulfilled need for family planning or unmet needs. The number of unmet needs in Indonesia is still high, at 10.50 %. This study aims to determine the differences between unmet needs in reproductive-aged women for family planning.*
Methods: *This study was descriptive-analytic conducted from December 2019 to January 2020 at Dr. Iskak Hospital, Tulungagung, Indonesia.*
Results: *There was a significant difference between the unmet need classification of unplanned pregnancy and childbirth delivery of reproductive-aged women and unpregnant, unplanned and undetermined childbirth delivery of reproductive-aged women, including age (p= 0.030), number of children (p= 0.031), an education level (p= 0.030), spouse support (p= 0.016), history of family planning usage (p= 0.017), and history family planning's side effect (p= 0.001). However, the work status and income level results showed no significant differences between both groups (p= 0.615; p= 0.629; respectively).*
Conclusion: *Most unplanned pregnancy and childbirth delivery of reproductive-aged women are poor educated with few children and do not have sufficient knowledge about contraception.*

Keywords: *Unmet need, family planning, reproductive aged women, pregnant.*

RESUMEN

Introducción: *Un factor que condujo al aumento de la población fue la necesidad insatisfecha de planificación familiar o las necesidades insatisfechas. El número de necesidades insatisfechas en Indonesia sigue siendo elevado, del 10,50 %. Este estudio tiene como objetivo determinar las diferencias entre las necesidades insatisfechas de planificación familiar en mujeres en edad reproductiva.*
Métodos: *Este estudio fue descriptivo-analítico realizado desde diciembre de 2019 hasta enero de 2020 en el Hospital Dr. Iskak, Tulungagung, Indonesia.*
Resultados: *Hubo una diferencia significativa entre la clasificación de necesidades insatisfechas de embarazo*

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no planeado y parto de mujeres en edad reproductiva, no embarazado y parto no planeado e indeterminado de mujeres en edad reproductiva, incluida la edad (p= 0,030), el número de hijos (p= 0.031), nivel de educación (p= 0.030), apoyo del cónyuge (p= 0.016), historial de uso de planificación familiar (p= 0.017) y antecedentes de efectos secundarios de planificación familiar (p= 0.001). Sin embargo, los resultados de la situación laboral y el nivel de ingresos no mostraron diferencias significativas entre ambos grupos (p= 0,615; p= 0,629; respectivamente).

Conclusión: *La mayoría de las mujeres en edad reproductiva, con embarazos y partos no planeados. tienen una educación deficiente, tienen pocos hijos y no tienen suficientes conocimientos sobre anticoncepción.*

Palabras clave: *Necesidad insatisfecha, planificación familiar, mujeres en edad reproductiva, embarazadas.*

INTRODUCTION

Indonesia's population will continue to increase over the next years. Based on the projections, Indonesia's population in 2010-2035 will be rising from 238.5 million to 305.6 million in numbers (1). Balanced population growth can be seen from the Total Fertility Rate (TFR), but it is feared that the TFR figure in Indonesia will not match the population projection in 2020, with the TFR figure reaching 2.1 (2). One of the factors causing an increased population is the unfulfilled need for contraception or the unmet need for family planning (3). Unmet need is a term for reproductive-aged women who want to control their pregnancy but do not use any contraception (4).

The increasing rate of unmet need will affect population explosion and affect Maternal Mortality Rate (MMR) in Indonesia (5). The reproductive-aged woman who is not using a family plan might have a high chance of getting pregnant and experiencing complications during pregnancy. This can be caused by the existence of abortion because of unwanted pregnancy, having too many deliveries, and complications after birth (6).

Indonesia has a program called Keluarga Berencana (KB) or family planning in handling unmet needs (7). The implementation of the family planning program and must be carried out comprehensively and through collaboration between sectors including cadres (8). However, according to the 2017 IDHS, the number of unmet needs in Indonesia is still quite high, at 10.50 percent, and has not met the strategic target, which refers to 10.26 percent for the unmet need number in 2017, so the concept of unmet need with such figures which are difficult to be reduced needs to be debated continuously through more effective and efficient breakthroughs (9). A study about forecasting of unmet need percentage in East Java, Indonesia using the Autoregressive Integrated Moving Average (ARIMA) method show that from December 2019 to February 2020, there was an increase in the number of unmet needs in East Java, Indonesia (10).

The category of reproductive-aged women of unmet need is divided into two, namely unplanned pregnancy and childbirth delivery of reproductive-aged women and unpregnant, unplanned, and undetermined childbirth delivery of reproductive-aged women. Those two categories relate to Communication, Information, and Education (IEC) interests on family planning issues to communities (11,12). Considering that Indonesia is currently experiencing population explosion threats and resulted for its high and far away targeted number of unmet needs, simple research that involves the perception of each no use of contraceptive and reproductive-aged women is needed. This study aims to determine the differences between unmet needs in reproductive-aged women for family planning.

METHODS

This research is a descriptive-analytic study with a cross-sectional design to see the characteristic of unmet need respondents by collecting data simultaneously. This research was conducted from December 2019 to January 2020. The populations in this study were policlinic patients and their escorts in Dr. Iskak Hospital, Tulungagung, Indonesia. The research samples consisted of 70 respondents of reproductive-aged women. The research instrument was arranged in the form of a questionnaire using Chi-Square test data analysis.

RESULTS

Table 1 displays differences in the distribution of age, number of children, education level, income level, spouse support, family planning history, and unpleasant history of using family planning factors. They indicated a homogenous and uniform on the observed samples. The samples which were examined on the employment status factors were significantly different from both the respondents who worked and did not work, with the result that the dominant respondents had employed.

Table 1

Distribution of respondents

Factor	Category	n	%	p
Age	≤ 35	39	56	
	>35	31	44	0.339
Number of	≤ 2	37	53	
Children	>2	33	47	0.633
Education Level	≤ High School	39	56	
	>High School	31	44	0.339
Employment	Yes	46	66	
Status	No	24	34	0.009*
Income Level	≤ Regional Minimum Wage	40	57	
	>Regional Minimum Wage	30	43	0.232
Spouse Support	Yes	40	57	
	No	30	43	0.232
History of Family	Yes	36	51	
Planning	No	34	49	0.811
History of Family	Yes	30	83	
Planning's Side	No	6	17	0.811
Effect				

Description: Superscript shows a meaningful difference

According to Table 2, receiving H0 probability was very low. Therefore, H0 was denied on ages, number of children, education level, spouse partner history of family planning usage, and unpleasant history of family planning's side effect factors. It means that there were fundamental differences between unplanned pregnancy and childbirth delivery of reproductive-aged women and unpregnant, unplanned, and undetermined childbirth delivery of reproductive-aged women in terms of age, the number of children, education level, spouse support, family planning history, and unpleasant side effect of family planning history. However, the results of the p-value on work status and income level showed that H0 was accepted, indicating no significant difference between unplanned pregnancy and childbirth delivery of reproductive-aged women with unpregnant, unplanned, and undetermined childbirth delivery of reproductive-aged women towards the employment status nor the income level.

Table 2

Characteristics of reproductive-aged women of Unmet Needs

Factor	Unplanned pregnancy and childbirth of reproductive aged women		Unpregnant, unplanned, delivery and undetermined childbirth delivery of reproductive aged women		p-value	OR
	n	%	n	%		
Age (years)					0.030*	2.909
≤ 35	24	62	15	38		
>35	11	35	20	65		
Number of children					0.031*	2.837
≤ 2	23	62	14	38		
>2	12	36	21	64		
Education Level					0.030*	2.909
≤ High school	24	62	15	38		
>High school	11	35	20	65		
Employment Status					0.615	0.776
Yes	22	48	24	52		
No	13	54	11	46		
Income Level					0.629	1.263
≤ Regional Minimum Wage	21	53	19	48		
> Regional Minimum Wage	14	47	16	53		
Spouse Support					0.016*	0.300
Yes	15	38	25	63		
No	20	67	10	33		
History of family planning						
Yes	13	36	23	64	0.017*	0.308
No	22	65	12	35		
History of Family Planning's Side Effect						
Yes	11	31	25	69	0.001*	0.183
No	24	71	10	29		

Description: Superscript shows a meaningful difference

DISCUSSION

This study found that age, number of children, education level, spouse support, history of family planning usage, and history of family planning's side effects had significant differences between the unmet need factors. However, there is no significant difference in work status and income level. The level in age risk during pregnancy and childbirth makes the tendency for women to choose the unmet need attitude of contraception, especially at high risk (>35 years). This is in line with several existing studies which show a relation between age and the unmet need for contraception (13,14). The most unmet need respondents were over 35 years of age because respondents did not use contraception due to the developed traditional assumption in society, which suggested that women are not reproductive

or were no longer fertile at that age. Moreover, the respondents thought that they are old and very unlikely to get pregnant. In addition, unmet need reproductive-aged women were more likely to have less than two children compared to those who have more than two children due to limited access to information about contraceptives on women with fewer children (15). Another study also revealed that women with one child have a lower need for contraception than women with more children (16).

For the education level factor, this study also explains the symptoms in society that the lower the education level, the lower the knowledge, awareness, and birth management level to the importance of contraceptives. In the end, the majority ignores the use of contraceptives to regulate births. This study strengthens the conclusions of the existing report that highly educated mothers have sufficient knowledge about family planning (KB) information. Therefore, the higher the education, the greater the chance of experiencing unmet needs because reproductive-aged women understand better about the impact and the risks, which will occur when using contraceptives (15,17).

Several studies have also revealed a link between spouse support and reproductive-aged women's decision to do unmet needs for family planning. A report showed a significant relationship between husband's support and the incidence of unmet need family planning in reproductive-aged women (18). There are several reasons for husbands prohibiting their wives from using contraceptives, mostly because of the side effects of family planning usage, such as impaired wife's health after using family planning. Besides, the husband's lack of information about family planning results in no directions for wives to use contraception because he wants a certain number of children. A study stated that several other reasons for unsupportive husbands in using contraceptives are religious reasons, high costs, and their side effects (18,19). Another report also revealed that many women say that their husbands are the main reason for not using contraceptives (20).

This study confirms that the reason for preventing reproductive-aged women from using contraceptives is because they have a history of using family planning in the past. This is in line with a report in East Java, Indonesia, that one factor that has a relationship with unmet needs in the history of family planning usage (21). Moreover, respondents who have a history of family planning have experienced side effects from contraceptive usage. the most frequent side effects experienced by the respondents are weight gain, menstrual cycles change, headache, nausea, and leg swelling (20).

Employment status has less impact on the choice of using unmet need family planning. The findings on the variable of employment status are consistent with the results of earlier studies. A report found that there was no significant relationship between work status and unmet need (22). However, this finding contrasts with the results of a study that mothers with working status have a more significant influence on the occurrence of unmet needs than those who are not working (14). Besides, the finding of this study indicates a bias in the opinion that the income level of reproductive-aged women is not related to the decision in using unmet need family planning. A report found that family income did not associate with the incidence of unmet need because families with incomes both below and above the Regional Minimum Wage experienced unmet need incidents (23). Income level is not a significant benchmark for the occurrence of unmet needs.

CONCLUSION

There was a significant difference between the characteristics of reproductive-aged women with unmet need for family planning regarding age, number of children, level of education, partner support, history of use of family planning, and unpleasant history in using family planning. However, there was no significant difference between reproductive-aged women's characteristics and the unmet need for family planning based on work status and income level.

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Conflict of Interest

No relevant disclosures.

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Karo Traditional Oil, a traditional herbal medicine from Indonesia promote wound healing acceleration by suppressing tumor necrosis factor - α and stimulating interleukin 10 production

El Aceite de Karo Tradicional, una medicina herbaria tradicional de Indonesia, promueve la aceleración de la curación de las heridas al suprimir el factor de necrosis tumoral - α y estimular la producción de interleucina 10

Nova Primadina[1*•]

SUMMARY

Introduction: *Wound healing acceleration is often found on open wounds smeared with Karo Traditional Oil, but its mechanism of action is unknown. Therefore, this study aimed to assess the mechanism of action of active compounds in Karo Traditional Oil in the inflammation phase of the wound healing process.*
Methods: *A randomized post-test-only control group design study was conducted on 54 male Wistar rats. The negative control was treated with NaCl moist gauze. The positive control was treated with Karo Traditional Oil's carrier oil gauze, the treatment group was treated with Karo Traditional Oil gauze and observed on the first, third, and seventh day.*
Results: *There was a significant increase in inflammatory cells on 1st-day post-treatment in the treatment group compared to the negative and positive control groups (p= 0.001). There was a significant decrease in Tumor Necrosis Factor - α (TNF- α) cytokines level on the first day (p= 0.002) and day-7 (p= 0.007). There was a significant decrease in Interleukin (IL)-10 cytokine level on the first day (p= 0.012), then a significant increase on the seventh day (p= 0.002).*
Conclusion: *Active compounds in Karo Traditional Oil acts as a potent inflammation regulator in the wound healing process by suppressing the pro-inflammatory cytokines and promoting anti-inflammatory cytokines.*

Keywords: *Karo Traditional Oil, wound healing, TNF-α, IL-10, inflammation cells.*

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RESUMEN

Introducción: *La aceleración de la cicatrización de heridas se ha observado a menudo en heridas abiertas untadas con el Aceite Karo Tradicional, pero su mecanismo de acción se desconoce. Por lo tanto, este estudio tuvo como objetivo evaluar el mecanismo*

de acción de los compuestos activos en el Aceite Karo Tradicional en la fase de inflamación del proceso de cicatrización de heridas.
Métodos: *Se llevó a cabo un estudio de diseño de grupo de control aleatorizado posterior a la prueba en 54 ratas Wistar macho. El control negativo se trató con una gasa húmeda de NaCl. El control positivo se trató con una gasa con el vehículo del Aceite Karo Tradicional, el grupo de tratamiento se trató con gasa con el Aceite Karo Tradicional y se observó en el primer, tercer y séptimo día.*
Resultados: *Hubo un aumento significativo de células inflamatorias en el primer día después del tratamiento en el grupo de tratamiento en comparación con los grupos de control negativo y positivo (p= 0,001). Hubo una disminución significativa en el nivel de citocinas como el factor de necrosis tumoral - α (TNF-α) el primer día (p= 0,002) y el día 7 (p= 0,007). Hubo una disminución significativa en el nivel de la citocina interleucina (IL) -10 el primer día (p= 0,012), la cual aumentó significativamente el séptimo día (p= 0,002).*
Conclusión: *Los compuestos activos en el Aceite Karo Tradicional actúan como un potente regulador de la inflamación en el proceso de curación de heridas al suprimir las citocinas proinflamatorias y promover las citocinas antiinflamatorias.*

Palabras clave: *Aceite Karo Tradicional, cicatrización de heridas, TNF-α, IL-10, células de inflamación.*

INTRODUCTION

Nowadays, wound healing is still an important issue among scientists, practitioners, and clinicians because as time goes by, the demands of society for wound healing and its management to achieve the maximum possible results are also higher. Both acute and chronic wounds require good wound care and management. The series of activities include cleaning the wound and changing the dressing (1). A study in Surabaya, Indonesia, shows that modern dressing in healing was better compared to classic dressing (2). One of the ultimate goals of wound healing is to speed up the process of re-epithelialization by controlling the inflammation phase.

The more complex wound problem can be seen from the increasing number of incidents of injuries every year. According to a study, there were 20 million acute traumatic wounds and lacerations (3). Recent research in the United States shows the prevalence of patients with injuries is 3.50 per 1 000 population, with the most significant cause of injury to the world's population is surgery/trauma injuries (48.00 %) (3). American Wound Association researched the incidence of wounds in the world based on the etiology of the disease. The most acute wound data were obtained: 110 300 000 surgical cases, 20 400 000 abrasions, 10 000 000 burns, and 1 600 000 trauma injuries (4). In Indonesia, the infection rate for surgical wounds reached 2.30, up to 18.30 % in 2001, and is currently increasing to 55.1 %. This phenomenon indicates the increasing number of wound healing complications that cause prolonged inflammatory processes, and the wound healing time cannot be estimated (5,6).

Open wounds, which take a long time to heal, are usually caused by the prolonged inflammation phase. A report stated that the application of cellulose is better than zinc oxide non-eugenol on the healing of open wounds after periodontal surgery (7). However, the longer the wound heals, the more susceptible it is to microorganisms exposure and the higher infection risk and complications of other diseases it will have. Increase treatment costs and are prone to cause functional and aesthetic problems such as the appearance of contractures, keloids, and hypertrophic scars (1,4,8).

Pharmacologically, the antiseptic drug that is often used for wound healing today is Povidone-iodine (9). However, povidone-iodine has a less significant effect on decreasing bacterial colonization in contaminated wounds, and some systemic side effects such as skin hypersensitivity reactions, swelling on the face also cause anxiety, depression, and myxoedema. Povidone Iodine is also corrosive and can damage fibroblast tissue. While the application of soft silicon dressing helps treat pain in wounds, it cannot accelerate wound healing, and the costs are quite expensive (10,11).

Experimental research concludes that Sukun leaf extract effectively increases collagen density in the healing process of excision wounds (12). A review stated that curcumin-loaded chitosan nanoparticle has the potential to accelerate the post-extraction wound healing in Diabetes Mellitus (DM) patients by decreasing Reactive Oxygen Species (ROS) levels in all stages of wound healing (13). A study also reveals that 10 % of standardized pomegranate extract

accelerates the healing of deep second-degree burn wounds (14). An empirical data on the use of Karo Traditional Oil shows that 42.86 % are wound treatments, and 99.3 % of them have been declared cured with results as expected. Components of the majority of Karo Traditional Oils consist of bicyclic monoterpene compounds with the most composition, 74.47 % composed of α-pinene compounds, which are known to have potent inflammatory regulatory effects so that they can accelerate the wound healing process phase (15). Therefore, this study aims to observe the mechanism of action of active compounds in Karo Traditional Oil in the inflammation phase of the wound healing process.

METHODS

Randomized post-test only control group design research on fifty-four male Wistar rats weighing 150 ± 30 g from Gajah Mada University Integrated Testing Research Institute Jogjakarta, Indonesia, was housed in an animal unit 23 oC least two weeks before the experiments. The rats were housed in individual cages, free access to water and food pellets, and divided randomly into nine groups.

The rat was injected with a 0.3 mL/100 x (weight in gram) Rat cocktail, consisting of Ketamin 2 mL, Xylazine 1.25 mL, ACP 0.33 mL, and NaCl 6.41 mL intramuscular. Square full-thickness wound was created on the right back of each rat with 2.5 x 2.5 cm size, and the negative control group was treated with Natrium Chloride (NaCl) moist gauze compresses, the positive control group treated with the gauze compresses of Karo Traditional Oil's carrier oil, treatment group treated with Karo Traditional Oil gauze compresses and observed on the first day, the third day, and the seventh day. The same person did all the procedures to minimize differences in the force of the person applies.

After the 7th day, all the rats were sacrificed, and the wound with surrounding tissues was separated and fixed in 10 % buffered formalin for 24 hours at room temperature. After fixation and dehydrated in grade ethanol, cleared in xylene, and embedded in paraffin, the sections were mounted in glass slides and stained with hematoxylin and eosin. Two pathologists inspected all slides without information to earlier treatment under magnifying instruments from x40 to x100 amplifications. The number of inflammatory cells counted by histopathological examination of Histological Examination (HE) painting, cytokine levels of Tumor Necrosis Factor- α (TNF- α) and Interleukin (IL) -10 counted by immunohistochemical examination.

Data were analyzed using ANOVA statistical test, followed by a post hoc multiple comparisons with SPSS 23 software, and are expressed as mean ± Standard Deviation (SD). The data were tested for normality and homogeneity. Statistical significance was accepted at $p < 0.05$.

RESULTS

Table 1 and Figure 1 show a significant increase in inflammatory cells on the first day post-treatment in the treatment group compared to the negative and positive control groups ($p = 0.001$).

Table 1

Inflammation Cells Count Analysis of the Studied Groups

Groups	First day Mean ± SD	Third day Mean ± SD	Seventh-day Mean ± SD
Negative control	0.47 ± 0.48 [a]	2.10 ± 0.68	157 ± 0.79
Positive control	1.13 ± 0.47 [b]	2.00 ± 0.93	2.07 ± 0.80
Treatment group	1.83 ± 0.56 [c]	2.00 ± 0.52	2.13 ± 1.00
P value	0.001*	0.786	0.484

* Statistically significant difference between a, b, and c
SD = Standard Deviation

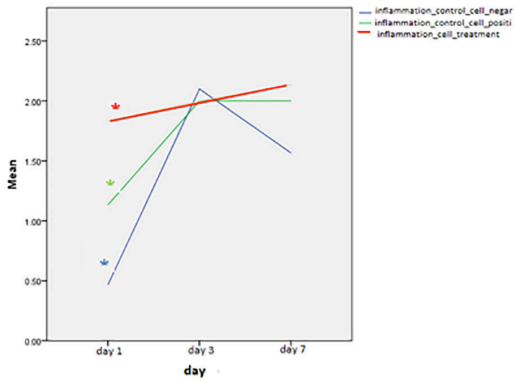

Figure 1. Inflammation cells count comparison graphic between the studied groups.

Table 2 and Figure 2 show a significant decrease in TNF-α cytokines level on the day-1 and day-7 day ($p=0.002$; $p=0.007$; respectively).

Table 2

TNF- α Cytokine level count analysis of the studied group

Groups	First day Mean ± SD	Third day Mean ± SD	Seventh-day Mean ± SD
Negative control	3.40 ± 1.18 [a]	1.50 ± 0.60	1.90 ± 0.41 [a]
Positive control	2.90 ± 0.84 [a]	1.53 ± 0.16	3.43 ± 1.47 [a]
Treatment group	1.33 ± 0.43 [b]	1.07 ± 0.53	0.90 ± 0.37 [b]
P value	0.002*	0.197	0.007*

*Statistically significant difference between [a] and [b]
SD = Standard Deviation

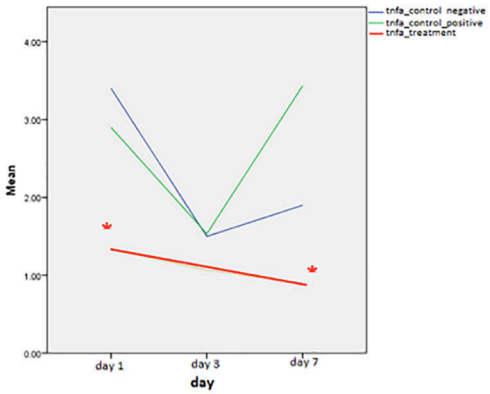

Figure 2. TNF- α cytokine level count comparison graphic between the studied groups.

Table 3 and Figure 3 show a significant decrease in IL-10 cytokines level on day-1 (p= 0.012), increasing significantly on the seventh day (p= 0.002).

Table 3

IL-10 Cytokine Level Count Analysis of The Studied Group

Groups Mean ± SD	First day	Third day Mean ± SD	Seventh-day Mean ± SD
Negative control	3.80 ± 1.81 [a]	3.33 ± 0.85	1.93 ± 0.88 [a]
Positive control	3.40 ± 1.02 [a]	3.67 ± 1.38	2.13 ± 1.06 [a]
Treatment group	1.43 ± 0.71 [b]	2.43 ± 0.75	4.47 ± 1.36 [b]
P value	0.012*	0.135	0.002*

*Statistically significant difference between a, and b
SD = Standard Deviation

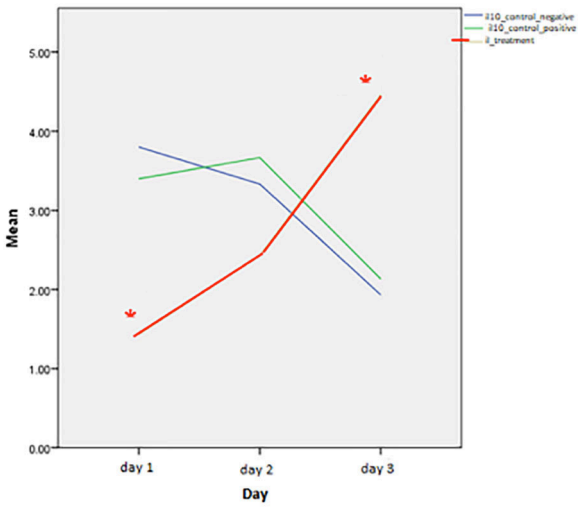

Figure 3. IL-10 cytokine level count comparison graphic between the studied groups.

DISCUSSION

Traditional Karo Oil regulates the inflammatory phase by accelerating the polarization of type-1 macrophages, marked by a decrease in the production of TNF-α pro-inflammatory cytokines significantly, into type-2 macrophages marked by an increase in the expression of IL-10 anti-inflammatory cytokines. The active ingredients of Karo Traditional Oils have been shown to regulate the inflammatory phase by suppressing the production of inflammatory cytokines characterized by low expression of pro-inflammatory cytokines TNF-α and IL-10 on the 1st post-treatment day 12, and stimulating the differentiation of monocyte cells and production of macrophage type-2 inflammatory cells and their activation, which is characterized by an increase in the anti-inflammatory cytokine IL-10 starting from the 1st to the 7th day after treatment while simultaneously releasing growth

factors which are the key regulation of the wound healing process (16,17). The α-pinene compound is a potent inflammatory regulatory compound, which is the main compound of Karo Traditional Oils regulating the inflammatory phase through inhibition of type-1 macrophages that express Cluster of Differentiation 86 (CD86) and pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 (16-18).

Inflammatory cells, especially those macrophages, play an essential role in the tissue repair process. Reduction in macrophage infiltration is closely related to the incidence of the prolonged wound healing phase (19). A significant increase in the number of inflammatory cells was found on the 1st post-treatment day in wounds treated with traditional Karo Oil compared to wounds treated with traditional Karo Oil solvent oil and wounds treated with PZ gauze, as shown in Figure.1. Typically, in wounds treated with PZ gauze, the inflammatory cells that come out first are neutrophil cells, and this will last for the first 72 hours after the wound occurs. The presence of neutrophil cells that extend in the wound will prolong the inflammatory phase because neutrophils release enzymes that degrade tissue so that the extracellular matrix deposit process and collagen synthesis to fill the wound tissue will be inhibited because the enzymes from these neutrophils degrade collagen (20). Meanwhile, this does not occur in wounds treated with traditional Karo Oil because the active ingredient content of this oil accelerating the change of neutrophils to macrophages in the first 24 hours and stimulates the differentiation of monocyte cells into inflammatory macrophage cells consistently from day 1 to day 7, which under normal circumstances began to occur on the 3rd day. This proves that the active compound in Karo Traditional Oils in the form of monoterpene compounds is a regulator of the inflammatory phase and also functions as a macrophage-activating substance (16,20).

The production of pro-inflammatory cytokines, in this case, represented by the low expression of TNF-α cytokines by type-1 macrophages from day 1 post-treatment to day 7 post-treatment showed a decreasing trend, whereas in the other two groups treated by solvent oil Karo Traditional Oils and moist gauze showed a decrease in pro-inflammatory cytokine TNF-α on day 1 to day 3 post-treatment and tended to increase again on day 7 post-treatment, as shown in Figure 2. α-pinene compounds and other terpene compounds from Karo Traditional Oils block the TLR 4 receptors on Iκβ kinase so that they inhibit Iκβ phosphorylation, this inhibits the activation of NFκβ, IKK-β, and MAPK suppression occurs through decreased MAPK phosphorylation (ERK and JNK) (21) so that the expression of pro-inflammatory mediators such as TNF-α is suppressed so as not to excess (22-24). TNF-α in this low level also plays a role in the re-epithelialization process by maintaining the stability of keratinocyte activation signals by cytokines IL-1 and stimulating K6 expression through transcription factors NFκβ and C/EBPβ and indirectly stimulating the secretion of cytokines FGF-7 by cells.

In this case, the content of bicyclic terpenes in traditional Karo oil, α-pinene, δ-3-carene, sabinene, and camphene has been shown to accelerate the resolution of inflammatory reactions through increased production of type-2 macrophages and anti-inflammatory compounds characterized by an increasing trend in expression. Cytokine IL-10 was significantly compared to the other two groups, from day-1 post-treatment to its peak at day 7 post-treatment, as shown in Figure 3 (17,22). The IL-10 cytokine is an anti-inflammatory cytokine to regulate the inflammatory phase, is anti-angiogenic, and a regulator of extracellular matrix deposition, which results in scar-free healing (25). With the discovery of a significant increase in the cytokine IL-10 on the 7th day, it is possible that wound healing in wounds treated by traditional Karo oil will be better aesthetically because it causes fine scars. Terpene compounds from traditional Karo oil stimulate TLR 3 receptors and inhibit the COX-2 pathway to stimulate the release of anti-inflammatory cytokines, this stimulates the polarization of macrophages from type-1 to type-2, and an anti-inflammatory response and healing process occurs (22). Therefore, it can be concluded that Karo Traditional Oils accelerates the polarization process of macrophage inflammation cells from Macrophages type-1 that express CD86 and pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and INF-γ, into type-2b macrophages, also known as type-2 macrophages or wound healing macrophages

that express CD 86 and the anti-inflammatory cytokine IL-10 with a significantly increased trend, growth factor TGF-β, and some MMP, and express the pro-inflammatory cytokine TNF-α, and IL-6 in small amounts.

The presence of type 2b macrophages expressing IL-10 and TGF-β will stimulate type 2c macrophages that express CD 206 and anti-inflammatory cytokines IL-10, MMP-9 IL-1β, and TGF-β in large amounts, and pro cytokines. -inflammatory IL-12 in small amounts, thus accelerating the transition of the wound healing process from the inflammatory phase to the proliferative phase where the wound treated with PZ gauze occurred after the 3rd day, but the wound treated with traditional Karo oil began to appear on the 3rd day (17,22,26).

CONCLUSION

Traditional Karo Oil regulates the inflammatory phase by accelerating the polarization of type-1 macrophages, marked by a decrease in the production of TNF-α pro-inflammatory cytokines significantly, into type-2 macrophages marked by an increase in the expression of IL-10 anti-inflammatory cytokines. As a result, it has been found that the re-epithelialization process in wounds smeared with Traditional Karo Oil since the third day after treatment and increased significantly on the 7th-day post-treatment.

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Conflicts of Interest

The authors declare no conflict of interest in this Traditional Karo Oil research.

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