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Elevated Systemic Immune – Inflammation Index for Predictor of Ulcerative Colitis: A Systematic Review and Meta-analysis

Sistema inmunológico sistémico elevado: índice de inflamación para predecir la colitis ulcerosa: una revisión sistemática y un metaanálisis

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SUMMARY

Introduction: *The Systemic Immune-inflammation Index (SII) is a simple, non-invasive, and low-cost parameter that has been studied to predict ulcerative colitis (UC). However, the result remains inconclusive. Therefore, this study aimed to confirm the utilization of SII in UC.*
Methods: *A systematic search was conducted. The inclusion criteria were articles that investigated the relationship between SII and UC and reported a specific cut-off value, specific sensitivity, specificity, and area under the curve (AUC). The odds ratio (OR) and mean difference (MD) using a 95 % confidence interval (CI) were used.*
Results: *Five studies enrolling 1386 patients were included. SII Index was significantly higher in UC patients (MD: 523.48 (95 % CI 303.89-743.07, P<0.00001). Furthermore, four studies were included in sensitivity, specificity, diagnostic odds ratio, cut-off values, and AUC analyses. The SII Index of 595.47 was the cut-off value for UC, with a sensitivity of 57 % and a specificity of 69 %. The AUC was 0.66 (95 % CI 0.61-0.70).*
Conclusion: *The SII index significantly increased in UC. Patients with SII >595.47 had odds of UC threefold greater than patients with lower SII.*

Keywords: *Ulcerative colitis, systemic immune-inflammation index, meta-analysis.*

RESUMEN

Introducción: *El Índice de Inflamación Inmune Sistémica (SII) es un parámetro simple, no invasivo y de bajo costo que ha sido estudiado para predecir la colitis ulcerosa (CU). Sin embargo, el resultado sigue sin ser concluyente. Por lo tanto, este estudio tuvo como objetivo confirmar la utilización de SII en CU.*
Métodos: *Se realizó una búsqueda sistemática. Los criterios de inclusión fueron artículos que investigaron la relación entre SII y UC e informaron un valor de corte específico, sensibilidad específica, especificidad*

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y área bajo la curva (AUC). Se utilizaron los odds ratio (OR) y la diferencia de medias (DM) utilizando un intervalo de confianza (IC) del 95 %.
Resultados: *Se incluyeron cinco estudios con 1 386 pacientes. El índice SII fue significativamente mayor en pacientes con CU (DM: 523,48 (IC del 95 %: 303,89-743,07, P<0,00001). Además, se incluyeron cuatro estudios en cuanto a sensibilidad, especificidad, razón de probabilidades diagnósticas, valores de corte y análisis de AUC. El índice SII de 595,47 fue el valor de corte para la CU, con una sensibilidad del 57 % y una especificidad del 69 %, el AUC fue de 0,66 (IC 95 % 0,61-0,70).*
Conclusión: *El índice SII aumentó significativamente en la CU. Los pacientes con SII> 595.47 tenían probabilidades de CU tres veces mayores que los pacientes con menor SII.*

Palabras clave: *Colitis ulcerosa, índice de inmuno-inflamación sistémica, metaanálisis.*

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition of the mucosal colon, which is associated with genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors (1). Incidence rates of UC vary considerably depending on the region. In 2017, UC incidence rates ranged from 0.97 to 57.9 per 100 000 in Europe, 8.8 to 23.14 per 100 000 in North America, and 0.15 to 6.5 per 100 000 in Asia and the Middle East (2). Nonetheless, with increasing urbanization and a shift from rural areas to cities, UC incidence in Asia has significantly risen (3).

The diagnosis of ulcerative colitis is made by clinical, endoscopic findings and histological evaluation. Determination of disease activity is essential in determining the patient's treatment (1). Imaging under endoscopy may accurately reflect the current inflammation of the intestines. Endoscopy biopsy is essential in determining a diagnosis, disease severity, treatment response, and recurrence (4). However, it is expensive, invasive, and weakly repeatable, and surgery may aggravate the disease (5). Hence, researchers continued to explore non-invasive measurements to determine the severity of UC and the level of inflammatory burden.

Several biomarkers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin (FC), and fecal lactoferrin (FL), are currently used for this purpose (6). Although CRP and ESR can help differentiate inflammatory from noninfectious conditions, these are nonspecific markers that can be increased in various other disease states (7,8). ESR is nonspecific and does not change as rapidly as CRP, further limiting its utility (7). While FC and FL levels are affected by bowel movements, different results can be obtained in the following days, and not practical to collect specimens (7,9,10). For these reasons, the search for a reliable, fast, and easy non-invasive method to determine the activity in ulcerative colitis continues.

The systemic immune-inflammation index (SII) is a simple, non-invasive, and low-cost biomarker of the inflammatory status and immune response. SII, combined with neutrophils, lymphocytes, and platelets, was first used in 2014 by Hu to evaluate the prognosis of hepatocellular carcinoma (HCC) (11). It is obtained by multiplying the neutrophil count and platelet count and dividing by the lymphocyte count. A higher SII value indicates a relatively low lymphocyte count and elevated neutrophil and platelet counts, demonstrating a more robust inflammatory response and weaker cell-mediated immunity (12). In recent years, SII has been used as a biomarker for predicting and assessing neuropsychiatric impairment, inflammatory disease, and cancer (13-15). Several studies have investigated the predictive value of SII in diagnosing UC. However, the result remains inconclusive.

This study aimed to determine the diagnostic test value of the SII in patients with clinical suspicion of UC. Our primary objective was to investigate whether SII can predict UC and distinguish between UC/active UC and non-UC/remission UC. Our second objective was to determine cut-off values of SII for UC and non-UC.

METHODS

This systematic review was performed according to an agreed predefined protocol. The study was conducted and presented according to Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) statement standards (16). The protocol for this study is registered in the international prospective register of systematic reviews (PROSPERO registration number CRD42022369714).

Eligibility criteria

This study included all observational studies reporting SII in participants of any age and gender with clinical suspicion or confirmed diagnosis of UC or active UC. Comparisons of UC or active UC versus non-UC or remission UC are considered in this study.

Studies were included if they met the following criteria: (a) the studies investigated the SII value in UC/active UC versus non-UC/remission UC; (b) a specific value of area under the curve (AUC) and a cut-off value divided the patients into high and low groups; (c) a specific diagnostic sensitivity and diagnostic specificity value; and (d) the studies had sufficient data to evaluate the diagnostic odds ratio (DOR).

Furthermore, articles were disqualified if they met the following criteria: (a) non-English study; (b) they were duplicate articles, reviews, conference summaries, and letters; (c) they were basic medical experiments, animal studies, case reports, and editorials; (d) the studies had unavailable data.

Search strategy

A systematic search of several online databases (Pubmed, SAGE Journals, Scopus, Web of Science, and Google Scholar) was performed on September 25, 2022, using the terms "(SII index OR systemic immune-inflammation index) AND ulcerative colitis".

Selection Process

Two authors independently screened the literature and identified relevant studies according to inclusion and exclusion criteria. Any disagreements were resolved by discussion with the third author.

Data Extraction

Two authors independently extracted the data from selected studies using Microsoft Excel. The following data were extracted from included studies: first author's name, year of publication, country, study design, study size and clinical condition of the study participants, sample size, clinical information of the study populations, and outcome data. The third author resolved any disagreements.

Quality assessment

Two authors used the Newcastle-Ottawa Scale to evaluate the quality of non-randomized studies in meta-analysis to determine the risk of bias (17). The quality of included studies was measured using three criteria: 1) selection, 2) comparability, and 3) outcome. The quality of the studies (good, fair, and poor) by awarding stars in each domain following the guidelines. A "good" quality score requires a selection score of 3 or 4 stars, a comparability score of 1 or 2, and an outcome score of 2 or 3. Two stars in the selection, one or two stars in comparability, and two or three stars in the results were necessary for a "fair" quality score. A "poor" quality score corresponded to a selection score of 0 or 1, a comparability score of 0 or 1, or an outcome score of 0 or 1.

Statistical analyses

For the primary objective of this study, we calculated the mean SII for each group in each comparison. Data are presented as mean differences (MD) and standard deviations (SDs). Median, sample size, range, or interquartile range were used to estimate mean and SD (18,19) The Stata 17 software was used for descriptive statistics, and the Review Manager 5.4 software was used for meta-analysis. The individual patient was used as the unit of analysis. Because of the anticipated clinical between-study heterogeneity, we used the random effects model for the analyses, and results were reported in a forest plot with 95 % confidence intervals (CIs).

Heterogeneity among the studies was assessed using the Cochran Q test (χ^2). We quantified inconsistency by calculating I^2 and interpreted it using the following guide: 0 %-50 % may represent low heterogeneity, 50 %-75 % may represent moderate heterogeneity, and 75 %-100 % may represent high heterogeneity. Pooled estimates for sensitivity, specificity, diagnostic odds ratio (DOR), and positive and negative likelihood ratios with the corresponding 95 % confidence interval (CI) were calculated using the Midas command in Stata 17 to measure the effectiveness of a diagnostic test. A summary receiver operating characteristic (SROC) curve was generated, and AUC analyses were used to describe overall accuracy as a potential summary of the SROC curve (20). Youden index statistic was used to identify the best predictive cut-off values (21).

Publication bias assessment

The Egger test assessed publication bias for a small study effect; $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of included study

A total of 75 records were found in our initial article search. After duplicates were excluded, 65 articles were screened, and five studies were assessed for eligibility. Five studies were included in the systematic review and meta-analysis. A flowchart of the included study is shown in Figure 1.

Characteristics of the five prospective single-center studies are presented in Table 1. Five studies enrolling 1 386 patients were included in pooled weight mean difference analysis (22-26), and four studies enrolling 984 patients were included in sensitivity, specificity, DOR, cut-off value, and AUC analyses (23-26). Three studies compared active UC versus remission UC (22-24), and two analyses UC versus non-UC (25,26). The optimal cut-off of SII in predicting UC ranges from 485.95 - 781.5.

Quality assessment

Quality assessment of all included studies was done using the Newcastle–Ottawa Scale. The assessments of studies are shown in Table 2. The overall quality of included studies was fair, but there was a study with poor quality.

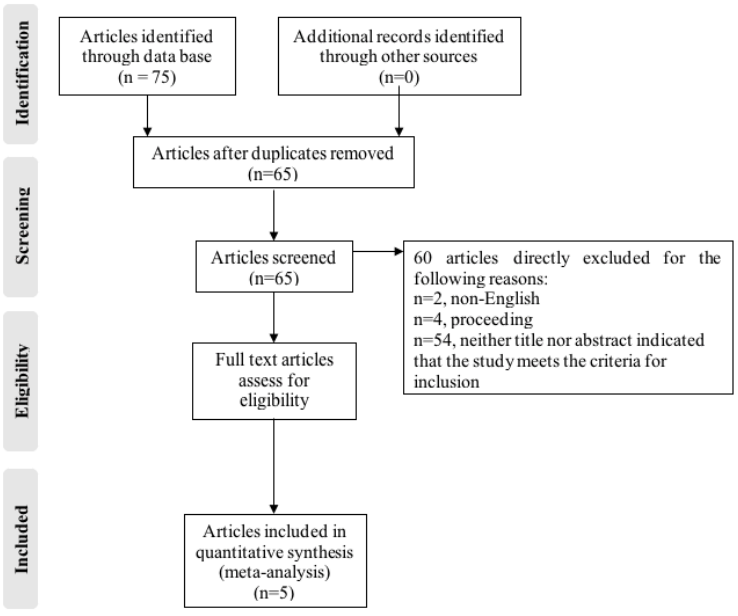

Figure 1. PRISMA flow chart of included studies.

Table 1. Baseline characteristic of included studies

First author	Year	Country	Study design	Study size (n)	Active UC	Control	Mean age	Centers	Optimal cut-off
Güven	2022	Turkey	Retrospective	402	237	165	47.4±13.7	Single	-
Lin	2022	China	Retrospective	187	151	36	47.4 ± 16.3	Single	595.47
Pakoz	2022	Turkey	Retrospective	81	47	34	44.0 ± 15.20 (active UC): 46.9 ± 13.5 (control)	Single	781.5
Xie	2021	China	Retrospective	362	187	185	41.94 ± 13.40 (active UC); 42.37 ± 10.70 (control)	Single	485.95
Zhang	2021	China	Retrospective	344	172	172	48 (35-57) (active UC); 47.50 (37-56) (control) *	Single	562.22

*Median (interquartile range)
Abbreviations: n, sample size; UC, ulcerative colitis

Table 2. Newcastle Ottawa Scale quality assessment

Items	Selection Adequacy of case definition	Representative of the cases	Selection of controls	Definition of controls	Comparability	Exposure Ascertainment of exposure	Same method of ascertainment	Non-Response Rate	Total scores	Quality assessment based on Ottawa scale
Güven (2022)	*	*	-	*	*	*	*	-	6	Fair
Lin (2022)	*	*	-	*	*	*	*	-	6	Fair
Pakoz (2022)	*	*	-	*	**	*	*	-	7	Fair
Xie (2021)	*	*	-	*	**	*	*	-	7	Fair
Zhang (2021)	*	*	-	*	*	*	*	-	6	Fair

Meta-analysis

The forest plot of SII value between patients with active UC/UC and control/remission UC is shown in Figure 2. SII was significantly higher in patients with active UC/UC (MD: 523.48 (95 % CI 303.89-743.07), p<0.00001). However, heterogeneity was significant (p<0.00001; I^2=95 %). The likelihood of publication bias was significantly based on the Egger test (p=0.0107).

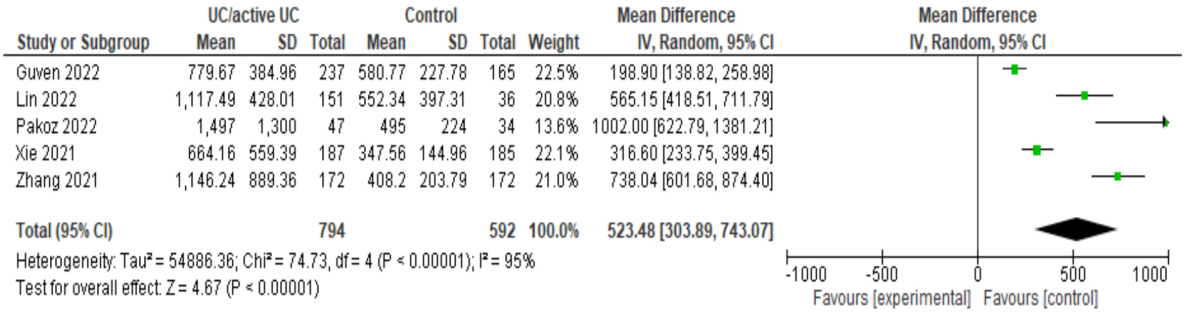

Figure 2. Forest plot of mean difference.

Accuracy of SII in predicting UC

Heterogeneity analysis showed that the sensitivity and specificity I^2 values were high ((92.00 (95 % CI 85.83-98.16), p<0.001) and (91.17 (95 % CI 84.18-98.16) p<0.001), respectively) and both p values were <0.001, indicating significant interstudy heterogeneity. The overall sensitivity and specificity of the SII in predicting UC were 57 % (95 % CI 45 % - 69 %) and 69 % (95 % CI, 49 %-84 %), respectively (Figure 3). The positive likelihood ratio, negative likelihood ratio, and DOR were 1.9 (95 % CI, 0.9-4.0), 0.61(95 % CI, 0.37-1.0), and 3 (95 % CI, 1-11), respectively. The Youden index determined the optimum SII cut-off as > 595.47. SROC analysis plot is shown in Figure 4. The AUC was 0.66 (95 % CI 0.61-0.70), implying that the SII was poor discriminant to predict UC cases.

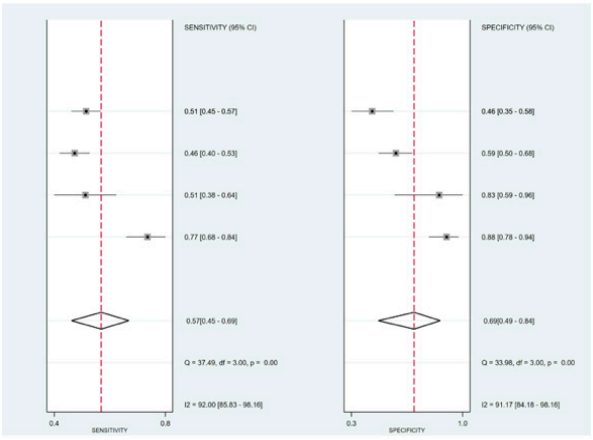

Figure 3. Forest plots for the sensitivity and specificity of the SII in predicting UC.

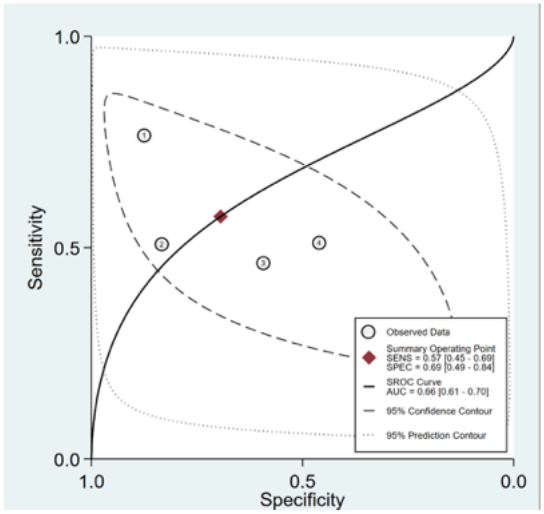

Figure 4. SROC curve of SII in all studies.

DISCUSSION

UC is a chronic inflammatory condition that frequently relapses. Several studies have reported relapse after clinical remission. Fukuda et al. reported a relapse rate of 26 % after two years in patients treated with 5-Aminosalicylic acids (5-ASA) (27). Bello et al. reported that 75 % of patients treated with mesalazine relapsed after 29 months of follow-up (28). Bots et al. reported that 18 of 24 UC patients relapsed in median 18 months follow-up after anti-TNF therapy withdrawal (29). Assessment to diagnosis is important to help the clinician monitor activity and determine therapy.

Truelove and Witts criteria scores are widely used for determining UC clinical remission. Nevertheless, the chief of these limitations are the ambiguous definitions of improvement and worsening and the lack of a severity score that can be tracked over time (30). Presently, colonoscopy and pathology biopsy remains the gold standard for determining the diagnosis and severity of ulcerative colitis (31). However, a severe case of UC is not a candidate for a colonoscopy since it could result in operation-related damage (32). Also, colonoscopy does not help predict disease recurrence in remission patients. Therefore, it is crucial to find a suitable non-invasive measurement.

An appropriate diagnosis and monitoring help the clinician to achieve and maintain the remission stage. Several examinations and biomarkers have already been established to help diagnose and monitor UC's severity. The simplest biomarker to detect the active stage suggested in Truelove – Witts's criteria is ESR and CRP. However, CRP and ESR will also increase quickly when tissue necrosis, infection, and other factors occur. Consequently, using it as a sole index to evaluate activity is insufficient (33). Other indicators should be used in addition to colonoscopy and other testing techniques.

The systemic immune-inflammation index (SII) is a simple, non-invasive, and low-cost biomarker of the inflammatory status and immune response. We performed this study to determine whether SII can predict UC/active UC. Our study showed that SII was significantly higher in patients with UC/active UC compared to those with non-UC/remission UC. Our results suggested that patients with SII value > 595.47 has odds of the UC/active UC happening threefold greater than patients with lower SII value. However, our SROC results show that the AUC is 0.66 (95 % CI 0.61-0.70), which means poor discrimination. This may be because SII may not be specific for UC, and SII values will be elevated in any inflammatory condition. So, focusing on the distribution of the future population with and without risk factors is necessary. This is because this risk distribution ultimately determines the risk distribution of cases/patients and controls/non-patients, which ultimately determines the ROC and AUC curves. A broader population risk distributions result in an enormous AUC of the ROC curve (34).

Other biomarkers extensively studied to predict UC are the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR). Similar to SII, NLR is a simple biomarker derived from hematological parameters. A meta-analysis by Ma et al., which included 11 articles, showed that the NLR of patients with UC was significantly higher than that of the control group (35). Nevertheless, this study did not perform diagnostic test accuracy analysis. Meanwhile, the summary study of PLR utilization in UC does not yet exist, so the results are inconclusive.

The major strengths of our study are the use of a more advanced statistical power approach and resolution to combine the outcomes of different analyses better understand the diagnostic accuracy of SII value for predicting UC. To our knowledge, our study is the first meta-analysis to investigate the predictive value of SII in UC.

There are some inadequacies in our study. First, only five articles were included in the meta-analysis, the number of participants in each study was relatively small, and the research addressed China and Turkey populations, which limits the universality of the population and may affect the conclusion. Second, the heterogeneity of the conclusion is high. Third, there was significant publication bias was observed in the Egger test.

Future studies comparing or combining the SII with other biomarkers such as NLR, PLR, and CRP might be needed to verify the most reliable one to predict relapse or active UC. In addition, a further meta-analysis with more studies in

prospective, multicenter, and large populations is also needed to confirm the diagnosis accuracy of SII.

CONCLUSION

The SII value of UC/active patients was significantly higher than in non-UC/remission UC. It is suggested that SII may be a valuable biomarker to predict the activity of UC. However, there are some inadequacies in our study. Further studies comparing or combining SII with other simple biomarkers such as NLR, PLR, and CRP might be needed to verify the best predictive value to predict UC/active UC. In addition, meta-analysis in prospective studies, multicenter, and large populations are needed to confirm the diagnosis accuracy of SII for predicting UC.

The Academic Collaboration of the Authors

Noer Halimatus Syakdiyah: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft.

Hendy Bhaskara Perdana Putra: Conceptualization, Methodology, Validation, Writing - original draft.

Noer Halimatus Sya'baniyah: Resources, Writing - original draft, Writing- review, and editing

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Conflicts of Interest

The authors declare no conflict of interest.

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