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Multimorbidity patterns and associated factors in hospitalized Venezuelan patients: a prospective study

Patrones de multimorbilidad y factores asociados en pacientes venezolanos hospitalizados: un estudio transversal

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SUMMARY

Background and Objective: *The recognition of the patterns in which diseases are grouped has been a growing research focus on multimorbidity. No data on this topic are available in Venezuela. The aim was to identify multimorbidity patterns in adult patients and to determine risk factors for multimorbidity patterns.* **Patients and Methods***: A cross-sectional study was conducted including adult patients hospitalized in the three Internal Medicine services at the main hospital in Ciudad Bolivar, Venezuela, between January and October 2019. Data regarding diagnoses were extracted from medical records while patients were hospitalized. These data were confirmed by questioning the patients and through a complete physical examination by two Internal Medicine specialists, to avoid errors due to underreporting of information.* **Results***: A total of 349 patients and 56 diseases were included, with 1 671 disease events being recorded, and a median of 4 (IQR 3) diseases per person. All patients had multimorbidity. Four multimorbidity patterns were detected. Pattern 1 (cardiorenal-hemodynamic), pattern 2 (cardiovascular), pattern 3 (pneumo-infectious-oncologic), and pattern 4 (diabetic). Younger age was a risk factor for patterns 1 and 3, whilst low socioeconomic status decreased the risk of belonging to pattern 2. No risk factors were found for pattern 4.* **Conclusion***: The burden of multimorbidity in hospitalized patients in Venezuela is high. Diseases are grouped into four different patterns, and although some pathophysiological explanations can be assumed, more information is going to be needed to try to explain these groupings, therefore future research on this topic must be carried out.*

Keywords: *Multimorbidity, patterns, risk factors, Venezuela.*

RESUMEN

Antecedentes y objetivos: *El reconocimiento de los patrones de agrupación de las enfermedades ha sido un foco de investigación creciente en la multimorbilidad.*

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En Venezuela no se dispone de datos sobre este tema. El objetivo fue identificar los patrones de multimorbilidad en pacientes adultos y determinar los factores de riesgo de los patrones de multimorbilidad. **Pacientes y Métodos:** *Se realizó un estudio transversal que incluyó pacientes adultos hospitalizados en los tres servicios de Medicina Interna del principal hospital de Ciudad Bolívar, Venezuela, entre enero y octubre de 2019. Los datos relativos a los diagnósticos se extrajeron de las historias clínicas mientras los pacientes estaban hospitalizados. Estos datos fueron confirmados mediante el interrogatorio de los pacientes y a través de un examen físico completo realizado por dos especialistas en Medicina Interna, para evitar errores por subregistro de información.* **Resultados:** *Se incluyeron 349 pacientes y 56 enfermedades, registrándose 1 671 eventos de enfermedad y una mediana de 4 (RIQ 3) enfermedades por persona. Todos los pacientes tenían multimorbilidad. Se detectaron cuatro patrones de multimorbilidad. El patrón 1 (cardiorrenal-hemodinámico), el patrón 2 (cardiovascular), el patrón 3 (neumo-infeccioso-oncológico) y el patrón 4 (diabético). La menor edad fue un factor de riesgo para los patrones 1 y 3, mientras que el bajo nivel socioeconómico disminuyó el riesgo de pertenecer al patrón 2. No se encontraron factores de riesgo para el patrón 4.* **Conclusiones:** *La carga de multimorbilidad en los pacientes hospitalizados en Venezuela es elevada. Las enfermedades se agrupan en cuatro patrones diferentes, y aunque se pueden asumir algunas explicaciones fisiopatológicas, se va a necesitar más información para tratar de explicar estas agrupaciones, por lo que se deben realizar futuras investigaciones sobre este tema.*

Palabras clave: *Multimorbilidad, patrones, factores de riesgo, Venezuela.*

INTRODUCTION

In recent decades, clinical guidelines with improved diagnostic and therapeutic strategies for the management of individual chronic diseases have been developed (1,2), which has significantly improved the life expectancy of the world's population (3). However, as the prevalence of multimorbidity —the presence of more than one chronic disease in an individual (4)— increases (5), and its concept becomes more refined (6), new challenges arise for healthcare workers who must navigate complex and specialized care pathways when treating patients with multimorbidity (7). The care of these patients requires more clinical expertise, greater use of diagnostic procedures and therapeutic interventions, better management of potential functional and/or cognitive disabilities, and greater coordination between professionals and/or levels of care, than those require for patients with a single disease (8).

In primary care, multimorbidity is considered the norm rather than the exception (9), with an estimated prevalence ranging from 13 %-95 % depending on the age group and methodology used (5,10,11), and involves differences between demographic characteristics and types of diseases (12,13). Multimorbidity is highly prevalent among the elderly, women, and people with low socioeconomic status, but is not exclusive to these groups (5,14-16). Patients with multimorbidity often have more frequent and prolonged hospitalizations (17), reduced functional status (18), high levels of polypharmacy (19), poorer quality of life (20), high health care costs (21), and increased mortality (22,23), which directly impacts the person's every-day life and also translates into an enormous economic burden both for the patient and the health care systems. Therefore, multimorbidity is of extraordinary importance, not only for the population but also for health systems (24).

The existence of chronic diseases that are systematically associated with each other, forming what are called multimorbidity patterns (25), has been widely investigated in recent years. Despite the diversity of populations and methodologies, some studies have consistently described three common patterns of multimorbidity: cardiovascular-metabolic, psychogeriatric, and musculoskeletal (14,24-30). Other research has observed different patterns between low- and middle-income countries with respect to high-income countries, related to socioeconomic status and other characteristics (31). However, certain patterns of multimorbidity are common in several countries, probably due to shared underlying biological processes or risk factors (32). Thus, reliable identification of multimorbidity patterns is a critical step in the development of health services sensitive to the health needs of these patients (33).

Understanding how diseases tend to cluster in the form of multimorbidity patterns could provide

useful information on common underlying pathophysiological mechanisms and generate new hypotheses (28). However, studies on this topic are scarce in Latin America (34,35). A recent Venezuelan study described five patterns of multimorbidity in hospitalized older patients, of which the most frequent were cardio-renal-metabolic in all older age and sex groups (unpublished data from postgraduate thesis). Multimorbidity patterns have not yet been described in the general hospitalized population in Venezuela. The primary objective of this study was to identify multimorbidity patterns in adult patients hospitalized in the Internal Medicine services of the main referral hospital in southern Venezuela during 2019. The secondary objective was to determine the risk factors associated with these multimorbidity patterns. We hypothesized that, in addition to the expected prevalent combinations, we could identify other prevalent but less obvious combinations of comorbidities.

METHODS

Patients and study design

A cross-sectional, prospective, non-experimental, descriptive study was conducted including adult patients hospitalized in the three Internal Medicine services of the University Hospital Complex "Ruiz y Páez", in Ciudad Bolivar, Venezuela, between January and October 2019. The sampling method was non-probabilistic, purposive.

Data collection

Data was extracted regarding diagnoses from the medical records while the patients were hospitalized in the Internal Medicine services. These data were confirmed by questioning the patients (or their family members if the latter was unable to complete the questioning due to some incapacitating medical or cognitive condition) and through a complete physical examination by two Internal Medicine specialists, to avoid errors due to underreporting of information. We defined multimorbidity according to its most common definition: the presence of two or more chronic diseases (5,36). We included age, sex, race, and education level as demographic characteristics.

Statistical analysis

Patient data were summarized using the following descriptive statistics: mean, standard deviation (SD), median, interquartile range [IQR], and/or absolute and relative frequencies, as needed. The distribution of variables was assessed using the Kolmogorov–Smirnov test. To obtain multimorbidity patterns, the hierarchical cluster analysis technique was used with Ward's method using squared Euclidean distance. Only diagnoses with ≥ 2 % frequency were taken into consideration. Subsequently, the agglomerations were plotted using a dendrogram that made it possible to appreciate the groupings at each level. Risk factors were determined by multinomial logistic regression. Statistical analysis was performed using Statistical Package for the Social Sciences version 26 (International Business Machines Corporation, Armonk, NY, USA). Values of $p<0.05$ were considered significant.

RESULTS

Characteristics of patients with multimorbidity

During the study period, a total of 349 patients were included in the analysis. The mean age was 52 (SD — standard deviation — 18; range: 18-97) years, the majority (55.6 %) were female, of mixed race (86.2 %), and with low socioeconomic status (94.8 %). All patients had multimorbidity (Table 1).

Patterns of patients with multimorbidity

A total of 101 diseases were recorded. Forty-five diagnoses were excluded because their frequency was less than 2 % (Table 1). Of the 56 diseases included, arterial hypertension was the most frequent (53.9 %). Figure 1 represents, employing a dendrogram, the agglomeration of patient diagnoses in multimorbidity patterns. The dendrogram is analyzed on the 10th level of rescaled distance cluster combine, generating four multimorbidity patterns.

Table 1

Characteristics of adult hospitalized patients

n = 349	
Age, mean (SD), years	52 (18)
≤ 25 years, n (%)	33 (9.5)
26-35 years, n (%)	45 (12.9)
36-45 years, n (%)	41 (11.7)
46-55, years, n (%)	71 (20.3)
56-65, years, n (%)	71 (20.3)
66-75 years, n (%)	51 (14. 6)
≥ 76 years, n (%)	37 (10.6)
Sex, female/male (%)	194/155 (55.6/44.4)
Race, n (%)	
Indigenous	5 (1.4)
White	34 (9.7)
Mestizo	301 (86.2)
African-Venezuelan	9 (2.6)
Education level, n (%)	
Illiterate	29 (8.3)
Literate with no education	40 (11.5)
Primary	127 (36.4)
High school	99 (28.4)
University	54 (15.5)
Socioeconomic level, n (%)	
Low	331 (94.8)
Medium	18 (5.2)
Multimorbidity, n (%)	
Yes	349 (100)
No	0 (0)

Figure 1. Multimorbidity patterns in hospitalized adult patients. The figure was made using Statistical Package for the Social Sciences version 26 (International Business Machines Corporation, Armonk, NY, United States).

A total of 1 671 disease events were recorded. The median number of diseases per person was 4 (IQR — interquartile range — 3; min.: 2; max.: 14) diseases. Patterns were labeled according to their predominant diseases. Pattern 1 (cardiorenal-hemodynamic) included 14 diseases. Pattern 2 (cardiovascular) included three diseases. Pattern 3 (pneumo-infectious-oncologic) included 34 diseases. Pattern 4 (diabetic) included five diseases. The pattern with the highest number of disease events was pattern 1 with 791 (47.3 %) events, while pattern 2 had the highest median number of significant disease events with 85 (IQR 110) (Table 2).

The most frequent multimorbidity pattern was pattern 1, predominantly affecting 151 (43.3 %) patients. Pattern 3 predominantly affected 58 (16.6 %) patients, while 84 (24.1 %) had no predominant pattern but several patterns (Figure 2).

Risk factors associated with patterns of patients with multimorbidity

All sociodemographic variables studied were included in the model, except educational level, because with this variable included, the goodness of fit was very poor. According to

Table 2

Multimorbidity patterns according to the disease that make them up and disease events

Pattern	Diseases	n = 349	Disease events; n = 1 671	
			Total, n (%)	Median (IQR)*
1	Mild anemia	52 (14.9)	791 (47.3)	50.5 (35)
	Moderate anemia	86 (24.6)		
	Severe anemia	53 (15.2)		
	Ischemic heart disease	40 (11.5)		
	Hypertensive crisis	85 (24.4)		
	Hydroelectrolyte imbalance	80 (22.9)		
	Moderate dehydration	60 (17.2)		
	Chronic kidney disease	73 (20.9)		
	Ischemic stroke	23 (6.6)		
	Skin and soft tissue infection	49 (14.0)		
	Urinary tract infection	45 (12.9)		
	Acute kidney injury	28 (8.0)		
	Hypertensive nephropathy	38 (10.9)		
	Community-acquired pneumonia	79 (22.6)		
2	Hypertensive heart disease	40 (11.5)	306 (18.3)	85 (110)
	Arterial hypertension	188 (53.9)		
	Heart failure	78 (22.3)		
3	Adenocarcinoma (any type)	12 (3.4)	414 (24.8)	10.5 (7.00)
	Bicytopenia	7 (2.0)		
	Oropharyngeal candidiasis	16 (4.6)		
	Depression	17 (4.9)		
	Pericardial effusion	8 (2.3)		
	Bilateral pleural effusion	19 (5.4)		
	Right pleural effusion	15 (4.3)		
	Left pleural effusion	13 (3.7)		
	Mild dehydration	9 (2.6)		
	Severe dehydration	13 (3.7)		
	Protein-calorie malnutrition	19 (5.4)		
	Acute diarrheal disease	7 (2.0)		
	Chronic diarrheal disease	10 (2.9)		
	Chronic obstructive pulmonary disease	14 (4.0)		
	Upper digestive hemorrhage	8 (2.3)		
	Hydronephrosis	8 (2.3)		
	Hemorrhagic stroke	8 (2.3)		
	Non-Hodgkin's lymphoma	11 (3.2)		
	Nephrolithiasis	8 (2.3)		
	Systemic lupus erythematosus	7 (2.0)		
	Meningitis	10 (2.9)		
	Dilated cardiomyopathy	17 (4.9)		
	Morbid obesity	12 (3.4)		
	Diabetic foot	10 (2.9)		
	Sepsis	9 (2.6)		
	Cardiorenal syndrome	10 (2.9)		
	Convulsive syndrome	9 (2.6)		
	Frailty syndrome	15 (4.3)		
	Organic wasting syndrome	37 (10.6)		
	Acquired immunodeficiency syndrome	18 (5.2)		
	Low urinary obstructive syndrome	12 (3.4)		
	Uremic syndrome	7 (2.0)		
	Abnormal conduction disorders	8 (2.3)		
	Arrhythmias	11 (3.2)		
4	Diabetes mellitus type 2	62 (17.8)	160 (9.6)	25 (25.5)
	Peripheral vascular disease	31 (8.9)		
	Diabetic nephropathy	22 (6.3)		
	Diabetic neuropathy	25 (7.2)		
	Diabetic retinopathy	20 (5.7)		

*Medians are significantly different between the patterns ($p<0.001$; median test = 36.2; gl = 3).

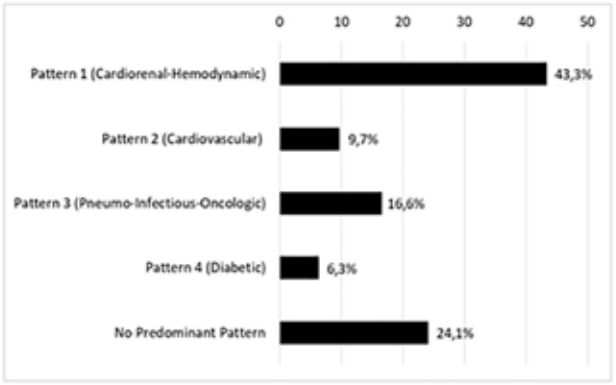

Figure 2. Frequency of multimorbidity patterns in hospitalized adult patients. The figure was made using Microsoft® Excel® version 2019 (Microsoft, Redmond, WA, United States).

the model ($p = 0.025$; goodness of fit: 0.11; R^2 Nagelkerke: 0.084), for pattern 1, age was an associated risk factor; that is, as age decreased by one year, the risk of presenting pattern 1 of multimorbidity increased by 2 %. For pattern 2, socioeconomic status was a risk factor; that is, having a low socioeconomic status decreases the risk of presenting multimorbidity pattern 2 by 79 %. For pattern 3, age was an associated risk factor; that is, as age decreases by 1 year, the risk of presenting multimorbidity pattern 3 increases by 2 %. No risk factors were found for multimorbidity pattern 4.

DISCUSSION

Multimorbidity poses major challenges at all levels of care. To our knowledge, this is the first study to identify and quantify multimorbidity patterns, as well as their risk factors, using cluster analysis in a representative sample of adult patients hospitalized in Internal Medicine services in Venezuela. One hundred percent of the patients were multimorbid, with a median of four diseases. Advanced age and low socioeconomic status were the associated risk factors for multimorbidity status. This study fills a previous gap of descriptive and quantitative data on the burden of multimorbidity in adult patients hospitalized in Internal Medicine services in Venezuela.

The characteristics of our studied patients did not differ from those of other populations with similar contexts. In our study, the mean age and predominance of the female sex were similar to several studies conducted in Latin America (34,35,37), Canada (13,38,39), and Europe (27,40-43). Relatively low educational levels have also been reported in the multimorbidity population in Latin America (34), here only 40 % had obtained a primary education, in agreement with our study. Likewise, the high frequency (86.2 %) of patients of mixed race found in our study was similar to that reported by other authors in Brazil (37). Prevalence rates of multimorbidity vary substantially among studies from various countries and continents, with reported rates ranging from 9 % to 99.%, depending on the setting and the number of conditions evaluated, with the highest rates found in hospital settings (63 %-99 %) (5,13,26,27,32,36,44-49). However, previous studies in Latin America have reported less variable prevalence rates, ranging from 12.4 % to 29.1 % (34,50,51). Our high prevalence rate of multimorbidity (100 %) was expected, by virtue of previous reports in elderly and patients with diabetes in the same institution (unpublished data from postgraduate thesis) and the high frequency of specialized diagnoses made in the context of our institution, which is a type-IV university hospital.

We found arterial hypertension as the most prevalent diagnosis (53.9 %), as in other studies conducted in Mexico (35), Spain (52), Italy (53), Switzerland (54), Sweden (55), and Indonesia (56). Likewise, the median number of diseases was 4 per patient. Except for one study in Spain that reported a higher median of seven (52), others conducted in the United States (57), Switzerland (40,54,57), and Israel (57) showed similar reports. Despite the growing international interest in evaluating multimorbidity patterns (25), particularly for hospitalized patients (27,45,54), data on this subject in Venezuela are scarce and unpublished. In our study, we identified four multimorbidity patterns, labeled according to their predominant diseases. Pattern 1 (cardiorenal-hemodynamic) consisted mainly of pathologies such as anemia, hypertensive crisis, and nephropathy, being the predominant pattern in 43.3 % of the patients

studied and with the highest number of disease events. A study conducted in Switzerland (54) identified a similar pattern (cardiorenal) in multimorbid patients hospitalized in Internal Medicine services. This found pattern may be explained by pathophysiological pathways or common risk factors, and because one disease may cause or result from the other (40,54,58). A relevant finding in pattern 1 is associated with age as a risk factor, being that, as age decreases by one year, the risk of presenting this pattern increases by 2 %. Studies on multimorbidity are always positively related to age (13,16,32,59,60), which is consistent with the notion that additional years of life constitute an opportunity to acquire other chronic conditions (5). This being so, the determination that a younger population is at greater risk of belonging to a multimorbidity pattern calls for a search for possible causal mechanisms or associated risk factors; however, this is beyond the scope of this study.

The analysis of pattern 2 of multimorbidity, revealed a strong cardiovascular predominance represented by arterial hypertension, heart failure, and hypertensive heart disease —all pathophysiologically related—, being the pattern with the highest median number of disease events. Although methodological differences between studies prevent a direct comparison, it is important to highlight that all studies on multimorbidity patterns report a cardiovascular pattern, whether or not associated with metabolic (5,24,25,27,40,42,43,52,55,61), renal (54), or respiratory (28,32) conditions. Interestingly, low socioeconomic status was associated with a 79 % decreased risk of presenting pattern 2 of multimorbidity. We did not find a description of the association between socioeconomic status and this specific (cardiovascular) multimorbidity pattern. However, the association between low socioeconomic status with higher prevalence of multimorbidity is well known (5,16,39,48,55,62-64). Further studies are needed to determine the factors favoring this inverse relationship. We hypothesize that lower purchasing power decreases access to probable risk factors yet to be determined but traditionally associated with heart disease (fast or junk food, alcohol, tobacco), which could favor the presence of diseases belonging to pattern 2 of multimorbidity.

Pattern 3 (pneumo-infectious-oncologic) included 34 diseases, whose grouping could be explained by shared pathophysiology (e.g., rhythm disorder, conduction disorder, and dilated cardiomyopathy), or a common risk factor (e.g., obesity, renal lithiasis, lower urinary obstructive syndrome, and cardiorenal syndrome), or because one of the diseases may be a consequence of the other (e.g., acquired immunodeficiency syndrome with oropharyngeal candidiasis, depression, chronic diarrheal disease, and organ wasting syndrome). Similar to pattern 1 (cardiorenal-hemodynamic), pattern 3 is associated with age as a risk factor, being that, as age decreases by one year, the risk of presenting such a pattern increases by 2 %. An interesting finding in this pattern was the presence of diabetic foot isolated from pattern 4 (diabetic), which includes type 2 diabetes mellitus and its other complications. This has been previously reported in older patients hospitalized in the same institution, where the diabetic foot was not included in the cardiorenal-metabolic pattern that included diabetes (unpublished data from postgraduate thesis). The persistence of this finding generates immediate recognition of the unique characteristics surrounding the diabetic foot syndrome, distinguishing it from other diabetic complications (65).

Pattern 4 (diabetic) describes type 2 diabetes mellitus as the main pathology, together with four complications of this disease. The pathophysiologic link between the entities in this pattern is evident. It should be noted that their presence in isolation from other diseases forming an individual pattern of their own, raises the possibility that the associations between diabetes and other diseases (that form other patterns) such as arterial hypertension and metabolic syndrome are defined by intrinsic aspects of these diseases, or by the presence of other factors not yet identified. Therefore, it is necessary to further study disease patterns in patients with diabetes and to continue studies already initiated as a basis.

During this study, some limitations were found regarding the availability of some diagnostic methods; however, all included diagnoses were confirmed and not presumptive. Finally, the reasons why the studied diseases are grouped in the already described patterns, merit more investigation, as well as the analysis of other variables that were not included in this study,

therefore, they are beyond the scope of the objectives set out in this research, given that we only sought to determine patterns and their constituent diseases. However, given the representative number of the sample and the applied statistical method, that made it possible to make evident groups of diseases that apparently did not group together, in addition to the determination of risk factors for the described patterns, these results can be generalized to patients admitted to Internal Medicine services in Venezuela hospitals with similar characteristics to ours, which is the main strength of this study.

CONCLUSIONS

The burden of multimorbidity in hospitalized patients in Venezuela is high. Diseases are grouped into four different patterns, and although some pathophysiological explanations can be assumed, more information is going to be needed to try to explain these groupings, therefore future research on this topic must be carried out.

List of abbreviations

SD: standard deviation; IQR: interquartile range.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Degree Work Commission of the "Dr. Francisco Battistini Casalta" Health Sciences School. The study was conducted in accordance with the ethical principles for medical research in humans of the Declaration of Helsinki and the Venezuelan regulations for this type of research, with the corresponding signed informed consent of all patients.

Consent for publication

All authors have given their consent for publication.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare no competing interests.

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Authors' contributions

MVM-R, VAF-B, and OCG-L conceived and designed the study. MVM-R, VAF-B, OCG-L, and LS collected clinical data. MVM-R, VAF-B, OCG-L, and FSC-N analyzed and interpreted the data. MVM-R and FSC-N wrote the manuscript. MVM-R, FSC-N, and LS critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

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