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Multimorbidity as a Risk Factor for Severity and Mortality in Patients With COVID-19: A Longitudinal Study in a Public Hospital in Southern Brazil

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Abstract

Background

Multiple chronic conditions are common in the population, and their impact on COVID-19 prognosis should be explored. This study aimed to investigate the association between multimorbidity and its patterns with severe outcomes in patients hospitalized with COVID-19 in a large hospital in southern Brazil.

Methodology

This retrospective cohort study, called NUTRICOVID19, included 1,173 patients (aged ⩾20 years) hospitalized with COVID-19 between June and December 2020. Multimorbidity, the main exposure, was evaluated in different ways: by the presence of ⩾2 or ⩾3 chronic health conditions, combinations of chronic conditions (dyads/triads), and multimorbidity patterns. Principal component analysis was used to derive the patterns. Poisson regression was used to investigate the association between the main exposure and adverse clinical outcomes, including intensive care unit (ICU) admission and invasive mechanical ventilation (IMV), whereas Cox proportional hazards regression was used to assess the association with mortality risk.

Results

Three multimorbidity patterns were identified: cardiometabolic, respiratory-cancer, and mental-endocrine. After adjustment for potential confounders, the cardiometabolic pattern and the hypertension/diabetes/cardiovascular disease triad increased the probability of ICU admission and IMV. Similarly, mortality risk was increased among individuals with multimorbidity (⩾3 chronic conditions) (hazard ratio (HR) = 1.47; 95% confidence interval (CI): 1.16-1.87), the hypertension/diabetes/cardiovascular disease triad (HR = 1.67; 95% CI: 1.24-2.23), and the cardiometabolic pattern (HR = 1.33; 95% CI: 1.04-1.70).

Conclusions

The combined cardiometabolic conditions were a risk factor for poor clinical progression or prognosis. Special attention should be given to COVID-19 patients with multimorbidity, considering its magnitude and specificities.

Categories: Cardiology, Epidemiology/Public Health, Infectious Disease
Keywords: covid-19, infectious disease, multimorbidity, multiple chronic conditions, principal component analysis, severity

Introduction

Coronavirus disease 2019 (COVID-19), an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in December 2019 in China and quickly spread throughout the world [1,2]. Most individuals infected with COVID-19 experience only mild symptoms, whereas approximately 15% develop severe disease requiring hospitalization and oxygen therapy, and about 5% progress to critical illness or death [1,2]. According to the literature, some of the main risk factors for serious complications and mortality are advanced age, male sex, and chronic diseases [3,4].

Several studies have shown that the presence of multiple chronic conditions has a greater impact on the clinical course of COVID-19 among hospitalized patients with SARS-CoV-2 infection than isolated chronic conditions, with the number of chronic conditions being linearly associated with disease severity [5,6].

Multimorbidity, defined as the coexistence of ⩾2 chronic conditions in the same individual, has been recognized as an important risk factor for frequent hospitalizations, prolonged hospital stays, and mortality. In addition, specific combinations of chronic conditions, including dyads, triads, and multimorbidity patterns, may also influence the prognosis of patients with COVID-19 [6-8].

A longitudinal study of patients hospitalized with COVID-19 found that the concomitant occurrence of certain chronic conditions, such as obesity, hypertension, hyperglycemia, and dyslipidemia, which are components of the metabolic syndrome and cardiometabolic multimorbidity patterns, has a similar clinical progression, including pro-thrombotic and pro-inflammatory events, in addition to systemic inflammatory markers (elevated C-reactive protein and interleukin-6) that could contribute to macrovascular complications, such as stroke and heart failure, leading to higher morbidity and mortality [9]. Furthermore, COVID-19-related myocardial injury and systemic vascular dysfunction may exacerbate pre-existing heart failure and contribute to adverse long-term cardiovascular outcomes [10]. A recent meta-analysis also demonstrated a 35% increased risk of new-onset heart failure following COVID-19 recovery, with follow-up extending up to 25 months after infection [11].

However, as far as we know, the relationship between multimorbidity and multimorbidity patterns and the prognosis of patients hospitalized with COVID-19 is a gap to be investigated in determining the evolution of this viral disease to contribute to the understanding of the underlying biological interactions between diseases and their clinical implications [7]. Thus, this study aimed to investigate the association between multimorbidity and multimorbidity patterns and severe outcomes (admission to the intensive care unit (ICU), invasive mechanical ventilation (IMV), and mortality) in COVID-19 patients admitted to a large public hospital in Porto Alegre, Rio Grande do Sul, Brazil.

Materials And Methods

Study design and population

This retrospective cohort study included adult and older patients (⩾20 years old) diagnosed with COVID-19 who were admitted to a hospital in Porto Alegre, Rio Grande do Sul, Brazil, between June and December 2020. It is part of a larger project called "NUTRICOVID19-Nutrition and its association with the prognosis of patients hospitalized for COVID-19 in Porto Alegre, RS," which was approved by the Hospital de Clínicas de Porto Alegre Research Ethics Committee (protocol: 2020-0388). The hospital is a reference center for moderate and severe cases of COVID-19.

The sample size was estimated considering obesity as the exposure (exposed-to-unexposed ratio of 0.4) and multiple outcomes (50% incidence among unexposed individuals), assuming a minimum detectable relative risk of 1.3, a 95% confidence level, and 80% statistical power. The initial estimated sample size was 924 participants, which was increased by 15% to account for potential losses, resulting in a minimum required sample size of 1,063 participants. The final study sample comprised 1,173 participants, exceeding the minimum sample size requirement.

In this study, all adults of either sex aged ⩾20 years who were diagnosed with COVID-19 through a positive reverse transcription polymerase chain reaction test and had been hospitalized in an inpatient or intensive care unit at the aforementioned hospital between June 1, 2020, and December 31, 2020, were included. Patients who remained hospitalized for <24 hours, who withdrew from treatment/hospitalization, pregnant women, and patients with missing weight and/or height data were excluded.

Study logistics

First, a pilot study was conducted with a sample of hospitalized COVID-19 patients at the institution before June 2020 to determine whether the questionnaire required adjustments or improvements. Final data collection began after the research team underwent training to standardize the application of data collection through electronic medical records. A detailed instruction manual was prepared to ensure standardized procedures. It should be noted that data were collected from medical records between October 2020 and July 2022, and each patient was included in the study only after completion of their hospital stay, when the final outcome (discharge or death) had already been determined.

Severe COVID-19 outcomes

In the present study, severe COVID-19 outcomes included clinical progression variables (ICU and IMV) and prognosis (mortality). Discharge or death was registered at the time of data collection.

Main exposures: multimorbidity and multimorbidity patterns

A total of 13 pre-existing chronic health conditions were initially investigated to assess multimorbidity, namely, arterial hypertension, diabetes mellitus, endocrine disease, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, a history of neoplasms, neurological disease, psychiatric illnesses, gastrointestinal disease, rheumatic/joint disease, and allergic disease. Multimorbidity was analyzed in different ways: (a) ⩾2 or ⩾3 chronic health conditions, (b) combinations of chronic

conditions (dyads/triads), and (c) multimorbidity patterns. Only pre-existing chronic health conditions with a prevalence of ⩾8% were included in the multimorbidity pattern analysis.

Exploratory variables

The sociodemographic and clinical data used as exploratory variables included sex, age (determined as date of birth minus the date of hospital admission and categorized as <60 and ⩾60 years), skin color (white, black, brown, yellow, or indigenous), which were categorized as white or black/brown (including the five yellow patients), education (categorized as incomplete elementary education, complete elementary education, complete secondary education, and complete higher education), type of hospitalization (public health system, private health system/health insurance), and place of residence (Porto Alegre, other cities). In the current study, obesity was treated as an independent exposure and was not included in the multimorbidity pattern analysis. The obesity variable was constructed using weight and height measurements collected on admission. These measurements were used to calculate body mass index (weight in kg divided by the square of the height in meters), with values ⩾30 kg/m² considered to indicate obesity.

Statistical analysis

Multimorbidity patterns were derived using principal component analysis (PCA). The selection of chronic conditions for PCA was based on their epidemiological relevance, prevalence in the study population (⩾8%), and the availability of information in hospital medical records. The obtained factors were orthogonally rotated (Varimax) to increase interpretability and ensure non-correlation between factors. As each chronic condition was coded as a dichotomous variable, the matrix of tetrachoric correlations between all conditions was calculated [12]. The number of factors retained was based on the following criteria: components with eigenvalues >1, the scree plot test, and factor interpretability [13,14]. Chronic conditions were considered to be loaded on a factor if they had an absolute correlation of ⩾0.3 with the factor [13,14]. Before PCA, the Kaiser-Meyer-Olkin test and Bartlett's sphericity test were performed to verify the applicability of the analysis [13]. Factor scores (i.e., individual factor values) were saved for each patient. The scores of each multimorbidity pattern were divided into tertiles [15] and categorized into low (first/second tertile) and high (third tertile).

The association between multimorbidity and the outcomes of ICU admission and IMV was investigated using Poisson regression with robust variance, a suitable method for analyzing complex samples. Thus, we obtained unadjusted and adjusted prevalence ratios with their respective 95% confidence intervals (CIs). Cox proportional hazards regression models were used to assess the independent association between the main exposures and in-hospital mortality, with results expressed as hazard ratios (HRs) and their respective 95% CIs. Follow-up time was calculated from hospital admission to hospital discharge or death.

Explanatory variables associated with the main exposures (multimorbidity and multimorbidity patterns) and the outcomes at $p \leqslant 0.20$ in the bivariate analyses were considered potential confounders. Multivariable analyses were performed only for associations between multimorbidity or multimorbidity patterns and ICU admission, IMV, or mortality that were statistically significant ($p < 0.05$) in the chi-square test for heterogeneity. Both Poisson and Cox proportional hazards regression models were fitted using three adjustment strategies: Model I (unadjusted), Model II (adjusted for sociodemographic variables), and Model III (adjusted for the variables included in Model II plus obesity). Statistical significance was set at p-values <0.05 for all analyses.

Missing data were handled using a complete-case approach. Patients with missing weight and/or height data were excluded during sample selection. Among the 1,173 patients included in the final study sample, education data were missing for 115 (9.8%) participants. These observations were excluded only from multivariable models that included education as an adjustment variable. No missing data imputation was performed. All statistical analyses were performed using Stata version 12.0 (StataCorp, College Station, TX, USA) and SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

In total, 1,574 patients had a confirmed diagnosis of COVID-19 during the study period. Of these, 401 did not meet the inclusion criteria; thus, 1,173 patients were included in the study. The mean age of the sample was 58.9 ± 14.9 years. Most were male, had white skin, had not completed high school, and lived in Porto Alegre. Almost all patients were hospitalized in the public health system. The most prevalent chronic conditions were hypertension, diabetes, cardiovascular disease, and chronic kidney disease. The outcome prevalences were ICU admission of 55.3% (95% CI: 52.5-58.2), IMV 40.7% (95% CI: 37.8-43.5), and mortality 26.5% (95% CI: 23.9-29.0) (Table *1*).

Variables	Sample distribution	ICU admission			IMV			Mortality		
	n (%)	n (%)	χ^2	P-value	n (%)	χ^2	P-value	n (%)	χ^2	P-value
		649			477			311		

Overall prevalence	1,173 (100)	(55.3)			(40.7)			(26.5)	
Sex									
Male	605 (51.6)	353 (58.4)	4.61	0.032	262 (43.3)	3.61	0.057	173 (28.6)	2.78	0.095
Female	568 (48.4)	296 (52.1)			215 (37.9)			138 (24.3)		
Age (years)									
20–39	148 (12.6)	63 (42.6)			36 (24.3)			16 (10.8)		
40–59	414 (35.3)	225 (54.4)	5.74	0.017	161 (38.9)	10.18	0.001	63 (15.2)	79.17	<0.001
60–79	517 (44.1)	317 (61.3)			253 (48.9)			190 (36.8)		
80–96	93 (8.0)	43 (46.2)			26 (28.0)			41 (44.1)		
Skin color									
White	954 (81.5)	513 (53.8)	5.43	0.020	379 (39.7)	1.96	0.162	239 (25.0)	5.53	0.019
Black/Brown	216 (18.5)	135 (62.5)			97 (44.9)			71 (32.9)		
Education*									
Complete higher	85 (8.0)	42 (49.4)			23 (27.1)			14 (16.5)		
Complete secondary	325 (30.7)	168 (51.7)	3.55	0.059	119 (36.6)	11.98	<0.001	65 (20.0)	23.44	<0.001
Complete primary	292 (27.6)	152 (52.0)			109 (37.3)			74 (25.3)		
Incomplete primary	356 (33.7)	207 (58.1)			164 (46.1)			124 (34.8)		
Residence									
Porto Alegre	687 (58.6)	384 (55.9)	0.25	0.620	270 (39.3)	1.35	0.246	175 (25.5)	0.96	0.327
Other cities	485 (41.4)	264 (54.4)			207 (42.7)			136 (28.0)		
Hospitalization type									
Public Health System	1,157 (98.6)	644 (55.7)	3.80	0.051	473 (40.9)	1.65	0.199	310 (26.8)	3.42	0.064
Private/health insurance	16 (1.4)	5 (31.3)			4 (25.0)			1 (6.3)		
Obesity									
No	686 (58.5)	369 (53.8)	1.58	0.209	278 (40.5)	0.01	0.908	210 (30.6)	14.25	<0.001
Yes	487 (41.5)	280 (57.5)			199 (40.9)			101 (20.7)		
Arterial hypertension									
No	514 (43.8)	257 (50.0)	10.51	0.001	186 (36.2)	7.60	0.006	110 (21.4)	12.27	<0.001
Yes	659 (56.2)	392 (59.5)			291 (44.2)			201 (30.5)		
Diabetes mellitus									

No	772 (65.8)	395 (51.2)	15.83	<0.001	288 (37.3)	10.56	0.001	176 (22.8)	16.00	<0.001
Yes	401 (34.2)	254 (63.3)			189 (47.1)			135 (33.7)		
Cardiovascular disease										
No	846 (72.1)	470 (55.6)	0.06	0.801	338 (40.0)	0.64	0.424	199 (23.5)	13.93	<0.001
Yes	327 (27.9)	179 (54.7)			139 (42.5)			112 (34.3)		
Chronic kidney disease										
No	990 (84.4)	552 (55.8)	0.47	0.491	401 (40.5)	0.07	0.795	251 (25.4)	4.38	0.036
Yes	183 (15.6)	97 (53.0)			76 (41.5)			60 (32.8)		

TABLE 1: Sample distribution and prevalence of ICU admission, IMV, and mortality according to sociodemographic and clinical characteristics in patients hospitalized with COVID-19 in a public hospital in southern Brazil (n = 1,173).

Pearson's chi-square test for heterogeneity was used for sex, skin color, residence, hospitalization type, obesity, arterial hypertension, diabetes mellitus, cardiovascular disease, and chronic kidney disease. The chi-square test for linear trend (Cochran–Armitage trend test, using equally spaced ordered scores) was used for age and education. Test statistics are χ^2 with 1 degree of freedom for trend tests and k − 1 degrees of freedom for heterogeneity tests.

*: Education: Data were missing for 115 participants.

ICU: intensive care unit; IMV: invasive mechanical ventilation

Table *1* also shows the distribution and prevalence of severe outcomes according to the investigated variables. The prevalence of ICU admission and IMV increased with age, was inversely proportional to education level, and was higher among patients with a history of chronic hypertension and diabetes. Black or brown skin color was related to higher ICU admission, and male sex was associated with a greater need for IMV. The mortality rate increased with age; was inversely proportional to education; increased with previous hypertension, diabetes, cardiovascular disease, and chronic kidney disease; and decreased with obesity (Table *1*).

Table *2* presents the derivation of multimorbidity patterns through PCA. We found a Kaiser-Meyer-Olkin coefficient of 0.612, with a significance of $p < 0.001$ in Bartlett's test, indicating that the analysis was adequate. Three multimorbidity patterns were identified, which explained 47.9% of the total variance: cardiometabolic (diabetes, hypertension, cardiovascular disease, and chronic kidney disease), respiratory-cancer (chronic lung disease and neoplasms), and mental-endocrine (psychiatric illnesses and endocrine disease). The cardiometabolic pattern had the highest percentage of variance (20.8%).

	Factors/Patterns		
	Cardiometabolic	Respiratory-cancer	Mental-endocrine
Diabetes mellitus	0.697	-0.118	0.055
Arterial hypertension	0.673	-0.326	-0.050
Cardiovascular disease	0.604	0.122	-0.119
Chronic kidney disease	0.515	0.179	-0.022
Neoplasms	-0.006	0.717	0.101
Chronic lung disease	-0.000	0.498	-0.151
Psychiatric illnesses	-0.096	-0.246	0.826
Endocrine disease	0.295	0.398	0.538
Explained variation (%)	20.8	14.4	12.9

TABLE 2: Factor load matrix for the three patterns of multimorbidity found in hospitalized COVID-19 patients aged 20 to 96 years in southern Brazil (n = 1,173).

Factor loadings indicate the strength of the association between each variable and each factor, with factor loadings <0.3 generally considered weak. The percentage of total variance accounted for by all factors is 48.1%.

Table 3 shows the prevalence of ICU admission, IMV, and mortality according to multimorbidity (⩾2 or ⩾3; dyads and triads) and multimorbidity patterns. The prevalence of ⩾2 conditions was 62.7% (95% CI: 59.9-65.4), and that of ⩾3 conditions was 35.1% (95% CI: 32.4-37.8). The most prevalent dyads were "hypertension/diabetes," "hypertension/cardiovascular disease," and "diabetes/cardiovascular disease"; the most prevalent triad was "hypertension/diabetes/cardiovascular disease." These results demonstrate the extent of cardiometabolic conditions in these groupings. Due to low prevalence, the other triads are not shown in the tables. The prevalence of ICU admission, IMV, and mortality was higher for patients with the "hypertension/diabetes" and "diabetes/cardiovascular disease" dyads, the "hypertension/diabetes/cardiovascular disease" triad, and high cardiometabolic pattern scores (Table 3).

Variables	Sample distribution	ICU admission			IMV			Mortality		
	n (%)	n (%)	χ^2	P-value	n (%)	χ^2	P-value	n (%)	χ^2	P-value
Multimorbidity (≥ 2)										
No	438 (37.3)	229 (52.3)	2.62	0.105	165 (37.7)	2.60	0.107	81 (18.5)	23.08	<0.001
Yes	735 (62.7)	420 (57.1)			312 (42.4)			230 (31.3)		
Multimorbidity (≥3)										
No	761 (64.9)	412 (54.1)	1.24	0.266	295 (38.8)	3.24	0.072	158 (20.8)	36.78	<0.001
Yes	412 (35.1)	237 (57.5)			182 (44.2)			153 (37.1)		
Specific chronic conditions (dyads)										
Hypertension/Diabetes										
No	852 (72.6)	434 (50.9)	24.27	<0.001	311 (36.5)	22.36	<0.001	193 (22.7)	23.82	<0.001
Yes	321 (27.4)	215 (67.0)			166 (51.7)			118 (36.8)		
Hypertension/CVD										
No	929 (79.2)	508 (54.7)	0.75	0.385	369 (39.7)	1.65	0.199	222 (23.9)	15.69	<0.001
Yes	244 (20.8)	141 (57.8)			108 (44.3)			89 (36.5)		
Diabetes/CVD										

No	1,017 (86.7)	550 (54.1)	4.82	0.028	398 (39.1)	7.42	0.006	242 (23.8)	28.99	<0.001
Yes	156 (13.3)	99 (63.5)			79 (50.6)			69 (44.2)		
Hypertension/CKD										
No	1,044 (89.0)	578 (55.4)	0.00	0.944	426 (40.8)	0.08	0.782	267 (25.6)	4.29	0.038
Yes	129 (11.0)	71 (55.0)			51 (39.5)			44 (34.1)		
Diabetes/CKD										
No	1,076 (91.7)	591 (54.9)	0.85	0.356	432 (40.2)	1.44	0.231	271 (25.2)	11.77	<0.001
Yes	97 (8.3)	58 (59.8)			45 (46.4)			40 (41.2)		
Specific chronic conditions (triad)										
Hypertension/Diabetes/CVD										
No	1,033 (88.1)	556 (53.8)	7.93	0.005	403 (39.0)	9.79	0.002	246 (23.8)	32.36	<0.001
Yes	140 (11.9)	93 (66.4)			74 (52.9)			65 (46.4)		
Multimorbidity patterns										
Cardiometabolic										
Low score	790 (67.3)	410 (51.9)	11.51	<0.001	292 (37.0)	13.75	<0.001	174 (22.0)	25.01	<0.001
High score	383 (32.7)	239 (62.4)			185 (48.3)			137 (35.8)		
Respiratory-cancer										
Low score	798 (68.0)	467 (58.5)	10.30	0.001	337 (42.2)	2.54	0.111	190 (23.8)	9.37	0.002
High score	375 (32.0)	182 (48.5)			140 (37.3)			121 (32.3)		
Mental-endocrine										
Low score	857 (73.1)	493 (57.5)	6.22	0.013	373 (43.5)	10.78	0.001	228 (26.6)	0.01	0.907
High score	316 (26.9)	156 (49.4)			104 (32.9)			83 (26.3)		

TABLE 3: Sample distribution and prevalence of ICU admission, IMV, and mortality according to multimorbidity and multimorbidity patterns in patients hospitalized with COVID-19 in a public hospital in southern Brazil (n = 1,173).

Multimorbidity: ≥2 and ≥3 chronic health conditions; Hypertension: arterial hypertension; diabetes: diabetes mellitus; CVD: cardiovascular disease; CKD: chronic kidney disease; Low score: first and second tertiles; High score: third tertile. Statistical test: Pearson's chi-square test (χ^2) for heterogeneity.

ICU: intensive care unit; IMV: invasive mechanical ventilation

Table 4 shows the unadjusted and adjusted prevalence ratios for the ICU and IMV outcomes according to multimorbidity and multimorbidity patterns. After adjustment in the multivariate models, the triad "hypertension/diabetes/cardiovascular disease" increased the probability of ICU admission and IMV by 5% and 10%, respectively. Among those with high cardiometabolic pattern scores, the probabilities of ICU admission and IMV were 15% and 21% higher, respectively. A higher respiratory-cancer pattern score was associated with a 17% lower likelihood of ICU admission.

Multimorbidity variables	ICU admission						IMV					
	Unadjusted PR (95% CI)	Wald z	P-value	Adjusted PR (95% CI)	Wald z	P-value	Unadjusted PR (95% CI)	Wald z	P-value	Adjusted PR (95% CI)	Wald z	P-value
Multimorbidity (≥3)				-								
No	1.00	1.11	0.261	-	-	-	1.00	1.83	0.069	1.00	1.30	0.188
Yes	1.06 (0.96-1.18)						1.14 (0.99-1.31)			1.11 (0.95-1.30)		
Specific chronic conditions (triad)												
Hypertension/Diabetes/CVD												
No	1.00	3.17	0.002	1.00	2.24	0.028	1.00	3.47	0.001	1.00	2.93	0.004
Yes	1.07 (1.03-1.12)			1.05 (1.01-1.10)			1.11 (1.04-1.17)			1.10 (1.03-1.17)		
Multimorbidity patterns												
Cardiometabolic												
Low score	1.00	3.43	<0.001	1.00	2.64	0.008	1.00	3.86	<0.001	1.00	2.45	0.016
High score	1.20 (1.08-1.33)			1.15 (1.04-1.28)			1.31 (1.14-1.50)			1.21 (1.04-1.41)		
Respiratory-cancer												
Low score	1.00	-3.20	0.002	1.00	-3.05	0.003	1.00	-1.65	0.117	1.00	-1.82	0.063
High score	0.83 (0.74-0.93)			0.83 (0.74-0.94)			0.88 (0.76-1.03)			0.86 (0.73-1.01)		
Mental-endocrine												
Low score	1.00	-2.42	0.017	1.00	-2.33	0.020	1.00	-3.02	0.002	1.00	-2.96	0.004
High score	0.86 (0.76-0.97)			0.86 (0.76-0.98)			0.76 (0.63-0.90)			0.76 (0.64-0.92)		

TABLE 4: Unadjusted and adjusted PRs and 95% CI for ICU admission and IMV according to multimorbidity and multimorbidity patterns in patients hospitalized with COVID-19 in a public hospital in southern Brazil (n = 1,173).

Low score: first and second tertiles; high score: third tertile. Associations were assessed using Poisson regression with robust variance; two-sided Wald z-tests. Model I: unadjusted prevalence ratio. Model II: adjusted for sex, age (<60 vs ≥60 years), skin color, and education. Model III: Model II additionally adjusted for obesity. In the adjusted models for IMV, obesity was not retained in the final model due to a lack of statistical significance.

ICU: intensive care unit; IMV: invasive mechanical ventilation; PR: prevalence ratio; CI: confidence interval; CVD: cardiovascular disease

Table *5* shows the unadjusted and adjusted HRs for mortality in hospitalized COVID-19 patients with multimorbidity. After adjustment in the multivariate models, the mortality risk was approximately 50% higher in those with multimorbidity involving ⩾3 chronic conditions (47%), the triad “hypertension/diabetes/cardiovascular disease” (67%), and the cardiometabolic pattern (33%).

Multimorbidity variables	Mortality								
Multimorbidity variables	Model I HR (95% CI)	Wald z	P-value	Model II HR (95% CI)	Wald z	P-value	Model III HR (95% CI)	Wald z	P-value
Multimorbidity (≥3)									
No	1.00	4.53	<0.001	1.00	3.11	0.002	1.00	3.16	0.002
Yes	1.68 (1.34-2.10)			1.47 (1.15-1.87)			1.47 (1.16-1.87)		
Specific chronic conditions (triad)									
Hypertension/Diabetes/CVD									
No	1.00	4.98	<0.001	1.00	3.18	0.001	1.00	3.43	0.001
Yes	2.01 (1.53-2.65)			1.61 (1.20-2.16)			1.67 (1.24-2.23)		
Multimorbidity patterns*									
Cardiometabolic									
Low score	1.00	3.76	<0.001	1.00	2.07	0.039	1.00	2.27	0.023
High score	1.54 (1.23-1.93)			1.30 (1.01-1.66)			1.33 (1.04-1.70)		
Respiratory-cancer									
Low score	1.00	3.03	0.003	1.00	2.79	0.006	1.00	2.40	0.014
High score	1.42 (1.13-1.78)			1.41 (1.11-1.80)			1.36 (1.06-1.75)		

TABLE 5: Unadjusted and adjusted HRs and 95% CI for mortality according to multimorbidity and multimorbidity patterns in patients hospitalized with COVID-19 in a public hospital in southern Brazil (n = 1,173).

Multimorbidity: ≥3 chronic health conditions; Hypertension: arterial hypertension; diabetes: diabetes mellitus; low score: first and second tertiles; Hhgh score: third tertile. Associations were assessed using Cox proportional hazards regression models; two-sided Wald z-tests. Model I: Unadjusted Cox proportional hazards regression model. Model II: Adjusted for sex, age (<60 vs. ≥60 years), skin color, and education. Model III: Model II additionally adjusted for obesity. Both multimorbidity patterns were included simultaneously in the multivariable regression models.

HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease

Cox regression was performed with independent models for each multimorbidity pattern (cardiometabolic and respiratory-cancer), generating similar results when the patterns were entered together in the multivariate model. Thus, they were not presented in the table.

Discussion

To our knowledge, this is the first study to investigate the associations of multimorbidity and multimorbidity patterns with severe COVID-19 outcomes. In this hospital-based study of patients aged 20 to 96 years, three multimorbidity patterns were identified: cardiometabolic, respiratory-cancer, and mental-endocrine. After adjustment in the multivariable models, multimorbidity and certain combinations and patterns of chronic conditions were associated with unfavorable COVID-19 outcomes. Multimorbidity involving ⩾3 chronic conditions was associated with a 47% higher hazard of mortality. The "hypertension/diabetes/cardiovascular disease" triad was associated with a 67% higher hazard of mortality and 5% and 10% higher prevalences of ICU admission and IMV, respectively. The cardiometabolic pattern, which also included chronic kidney disease, was associated with a 33% higher hazard of mortality and 15% and 21% higher prevalences of ICU admission and IMV, respectively. The respiratory-cancer pattern was associated with a 36% higher hazard of mortality, even after adjustment for the other patterns.

The presence of multimorbidity, regardless of the cutoff point, results in worse outcomes, such as hospitalization, longer hospital stay, and early mortality [8]. The association between multimorbidity and COVID-19 severity has been investigated in studies with hospitalized patients, which evaluated unfavorable prognoses, mainly mortality [5,16,17]. However, only one of these studies evaluated three outcomes, relating them to cardiometabolic conditions [5]. These studies showed that patients with ⩾2 chronic conditions had a higher risk of severe outcomes after COVID-19 infection. In our study, multimorbidity was associated with a higher occurrence of severe COVID-19 outcomes, consistent with findings from a cohort

study involving patients with diabetes [5]. One possible explanation for this finding is that immune dysregulation (i.e., changes that occur in the innate immune response of patients with chronic diseases) and increased inflammation may lead to worse clinical progression and worse prognosis in COVID-19 [18]. Evidence from cohort studies, although conducted with different populations, corroborates this hypothesis [19,20].

Certain combinations of chronic conditions are associated with severe outcomes, particularly those involving cardiometabolic conditions. Studies using different methodologies from ours found that dyads of chronic conditions that included hypertension, diabetes, cardiovascular disease, and chronic kidney disease were more prevalent [19-21] and were associated with severe cases of COVID-19 [6]. In the present study, dyads and triads including hypertension, diabetes, and cardiovascular disease were associated with the three severe outcomes. One possible explanation for this finding is that patients with preexisting conditions may have organ dysfunction, which becomes greater after SARS-CoV-2 infection and can involve complications such as heart, kidney, and multiple organ failure and death [6]. Studies have reported that the virus can cause direct damage to cardiac muscle cells, in addition to renal impairment, and the damage is potentially greater in patients admitted to the ICU [22,23].

The three identified multimorbidity patterns (cardiometabolic, respiratory-cancer and mental-endocrine) were similar to those detected in other studies, despite different methodologies for deriving the patterns [24,25]. The issue of multimorbidity patterns among COVID-19 patients has been little explored. In our review of the literature, we found a retrospective cohort of older adults (⩾70 years) with COVID-19 that identified three multimorbidity patterns: metabolic-renal-cancer (hypertension, diabetes, kidney disease, cancer, and chronic obstructive pulmonary disease), neurocognitive (cardiovascular disease, dementia, stroke, or vascular diseases), and unspecified (which included different chronic clinical conditions with prevalences ranging between 0 and 9%) [26]. Although the present study included adults aged ⩾20 years, whose prevalence of chronic conditions is lower than that of more advanced ages, the chronic condition patterns were similar. These findings suggest that similar multimorbidity patterns may be observed across different adult age groups and highlight their potential relevance to severe COVID-19 outcomes [27].

The literature indicates that certain combinations of chronic conditions are associated with a higher likelihood of severe COVID-19 outcomes. The present study identified that the cardiometabolic pattern was associated with greater ICU admission, IMV, and mortality. Our data corroborate the results of a study conducted in Italy, which found that patients with cardiometabolic multimorbidity (⩾2 risk factors for cardiovascular events such as diabetes, hypertension, or dyslipidemia) had a 3.19 times greater chance of the primary outcome (IMV, ICU admission, or mortality) compared to patients without cardiometabolic conditions [5]. A study conducted with public health system users in Spain found that individuals with a cardiometabolic profile were more likely to be hospitalized and die [20]. It is known that the chronic conditions that make up the cardiometabolic pattern are related to intense inflammatory processes and endothelial dysfunction, which can trigger different complications, such as venous and arterial thrombosis and multiple organ failure [28]. According to Maddaloni et al.(2020), these cardiometabolic conditions may share a common pathogenic basis or cooperate to predispose COVID-19 patients to progress to severe outcomes [5].

It is important to note that some multimorbidity patterns may be associated with a lower prevalence of certain severe COVID-19 outcomes, without necessarily indicating a protective effect. We found that patients with a high respiratory-cancer pattern score had a 17% lower probability of ICU admission. The specialized literature on clinical practice recommends that, in emergencies, patients should be managed differently according to certain individual characteristics, such as age. Due to the specific needs of older adults, their treatment must avoid invasive measures that are not urgent necessities [29]. Such clinical considerations may partially explain the lower prevalence of ICU admission observed among patients with high respiratory-cancer pattern scores, although this association should be interpreted cautiously. On the other hand, patients with high scores for this pattern had a 36% higher mortality risk. According to the literature, because it is a respiratory pattern due to underlying lesions in the lungs, worsening can occur suddenly and increase the risk of mortality [30]. Similar to other chronic conditions, those included in this pattern also share a common inflammatory background, which can trigger worse clinical outcomes [7]. Consistent with the literature, even on isolated diseases, other studies have reported that chronic lung disease [30,31] and neoplasms [32] are important risk factors for disease severity.

From a clinical perspective, our findings highlight the importance of early recognition of multimorbidity patterns, particularly the cardiometabolic pattern characterized by hypertension, diabetes, cardiovascular disease, and chronic kidney disease, as potential markers of increased risk for severe COVID-19 outcomes. In primary care settings, identifying these high-risk profiles may support proactive monitoring and appropriate management of pre-existing chronic conditions. Similarly, in hospital settings, recognizing these multimorbidity patterns may contribute to early risk stratification, closer clinical monitoring, and timely interventions aimed at preventing clinical deterioration. These findings may also inform healthcare preparedness strategies for future respiratory viral pandemics, although further studies are needed to evaluate the effectiveness of targeted interventions based on multimorbidity patterns.

This study's strengths include being a hospital-based, longitudinal study, with a large sample of adults and

older adults, assessing a robust set of information, and investigating an as-yet unexplored relationship between exposures and outcomes. In addition, the statistical method used to determine multimorbidity patterns did not establish a priori restrictions on the derivation of factors or on the number of factors to retain, which led to a better understanding of how the variables are grouped [13,15]. In addition, the study was conducted within a large hospital, a reference center for moderate-to-severe cases of COVID-19, which allows our findings to be generalized to this population. Finally, to our knowledge, this is the first study to investigate the associations of multimorbidity and multimorbidity patterns with severe COVID-19 outcomes, thereby expanding the current evidence on this topic. It is important to note that, although obesity is one of the major risk factors for noncommunicable chronic diseases, adjustment for obesity resulted in an even stronger association between the cardiometabolic pattern and severe COVID-19 outcomes, including mortality. This finding suggests that the association between the cardiometabolic pattern and unfavorable COVID-19 outcomes persists independently of obesity, consistent with previous studies [5,6]. Additional analyses of the study data will be conducted to investigate whether obesity acts as an effect modifier by testing its interaction with the main exposures and clinical outcomes.

Limitations

Although ours was a longitudinal study, i.e., robust in terms of causality criteria and focused on determining the temporality between exposure and outcome, some limitations should be considered when interpreting our findings. Data collection was limited by the retrospective nature of hospital records, including missing information. In addition, the exclusion of observations with missing data from adjusted analyses may have introduced selection bias and reduced statistical precision. Furthermore, the identification of pre-existing chronic conditions based on medical records, without systematic confirmation through objective clinical or laboratory measurements, such as glycated hemoglobin for diabetes mellitus, may have resulted in misclassification and potential information bias. The PCA method involves subjective decisions, such as the number of included chronic conditions, the cutoff point for factor loading [13,14], and the number of factors retained [13,14]. It should be noted, however, that each subjective decision was based on prior scientific knowledge [15], and each step of the analysis was described in detail. Additionally, the study was conducted at a single referral hospital during the early phase of the COVID-19 pandemic, when clinical management protocols and therapeutic approaches were evolving, potentially introducing unmeasured confounding. Moreover, ICU admission and the use of IMV may have been influenced by clinical decision-making, institutional protocols, and the availability of hospital resources, rather than solely reflecting disease severity. These factors, together with subsequent changes in viral variants, vaccination coverage, and clinical management, may limit the generalizability of our findings to more recent pandemic periods and current clinical settings.

Conclusions

This study demonstrated an association between multimorbidity and severe COVID-19 outcomes among hospitalized patients. Certain combinations and patterns of chronic conditions were associated with unfavorable clinical outcomes. In particular, the hypertension/diabetes/cardiovascular disease triad and the cardiometabolic multimorbidity pattern were associated with higher prevalences of ICU admission and IMV, as well as higher hazards of in-hospital mortality. These findings should be interpreted considering the observational nature of the study and the potential influence of residual confounding, selection bias, and clinical decision-making on the observed outcomes. Early identification and monitoring of patients with multimorbidity may contribute to improved clinical risk stratification and management. Further studies involving different populations and healthcare settings are needed to confirm these associations and assess their clinical implications.

Appendices

The original Portuguese and English-translated versions of the questionnaire are available at: https://docs.google.com/document/d/1eBzB5O5L1Ul1q8U54SWvonWUoRIHkKwt-dcJ2LieKy8/edit?usp=sharing

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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