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Variables associated with the clinical outcome of patients hospitalized with COVID-19

Variáveis associadas ao desfecho clínico de pacientes hospitalizados por COVID-19

Vagner Luís Desiderio[1], Vania Fabio[2], Evelin Capellari Cárnio[3], Simone de Godoy[4], Hadder Batista Silva[5], Leila Maria Marchi-Alves[6]

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ABSTRACT: Introduction: Understanding the pathophysiology of COVID-19 and factors associated with the severe evolution of this disease is essential for the development of better preventive, diagnostic, and therapeutic practices in the fight against the new coronavirus. Objective: Identify the sociodemographic and clinical characteristics associated with the clinical outcome of COVID-19 patients hospitalized in a private service in a city in the state of São Paulo. Method: This study analyzed sociodemographic and clinical data of 117 patients hospitalized with COVID-19, treated from July to December 2020. Data were analyzed using the non-parametric Pearson's chi-square test and Fisher's exact test, adopting a statistical significance level of 5% ($p<0.05$). Results: Most hospitalized patients were male, aged 61 to 70 years, who remained in the hospital for 8.7 days, and 29.9% of assessed patients died. Hypertension and low oxygen saturation were the most frequent comorbidity and severity factor, respectively. An association was identified between the variable 'outcome' and the variables 'age over 64 years' and 'altered renal function.' Conclusions: Among patients hospitalized with COVID-19, the clinical outcome was associated with the factors of severity, age group, and altered renal function.

Keywords: COVID-19; 2019-nCov New Coronavirus; Comorbidity; Measures of Association, Exposure, Risk or Outcome.

RESUMO: Introdução: Compreender a fisiopatologia da COVID-19 e fatores associados à evolução grave dessa doença é primordial para o estabelecimento de melhores condutas preventivas, diagnósticas e terapêuticas no combate ao novo coronavírus. Objetivo: Identificar as características sociodemográficas e clínicas associadas ao desfecho clínico de pacientes hospitalizados com diagnóstico de COVID-19 em um serviço privado de um município do interior paulista. Método: Incluíram-se os dados sociodemográficos e clínicos de 117 pacientes hospitalizados com diagnóstico de COVID-19, atendidos no período de julho a dezembro de 2020. Os dados foram analisados por meio do teste não paramétrico Qui-Quadrado de Pearson e o Teste Exato de Fisher, com adoção do nível de significância estatística de 5% ($p<0,05$). Resultados: A maior parte dos pacientes hospitalizados pertencia ao sexo masculino, com idade entre 61 a 70 anos, permaneceu em enfermaria por 8,7 dias sendo que 29,9% evoluíram para óbito. Hipertensão arterial e baixa saturação de oxigênio representaram, respectivamente, a comorbidade e o fator de gravidade mais frequentes. Identificou-se associação entre a variável desfecho com as variáveis idade superior a 64 anos e alteração da função renal. Conclusões: Entre pacientes hospitalizados com diagnóstico de COVID-19, o desfecho clínico associou-se aos fatores de gravidade, faixa etária e alteração da função renal.

Descritores: COVID-19; Novo Coronavírus 2019-nCov; Comorbidade; Medidas de Associação, Exposição, Risco ou Desfecho.

1. Clinical Director. Sermed Saúde Ltda. https://orcid.org/0000-0001-7211-9332. E-mail: vagnerdesiderio@sermedsaude.com.br.
2. Nurse. Quality Manager. Sermed Saúde Ltda. https://orcid.org/0000-0001-5501-6091. E-mail: vania.qualidade@sermedsaude.com.br
3. Full Professor. Ribeirão Preto College of Nursing at University of São Paulo. https://orcid.org/0000-0002-8735-4252. E-mail: carnioec@eerp.usp.br
4. PhD Professor. Ribeirão Preto College of Nursing at University of São Paulo. https://orcid.org/0000-0003-0020-7645. E-mail: sig@eerp.usp.br.
5. Graduate Student. Ribeirão Preto College of Nursing at University of São Paulo. https://orcid.org/0000-0002-0584-7425. E-mail: hadder.silva@usp.br
6. Associate Professor. Ribeirão Preto College of Nursing at University of São Paulo. https://orcid.org/0000-0001-9374-8074. E-mail: lmarchi@eerp.usp.br
Corresponding author: Leila Maria Marchi-Alves. Ribeirão Preto College of Nursing at University of São Paulo. Avenida dos Bandeirantes, 3900. Bairro Monte Alegre. Ribeirão Preto, SP, Brazil. CEP: 14.040-902.

INTRODUCTION

The coronavirus disease 2019, or COVID-19, is a disease of global distribution caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). From the first case, described in December 2019, until mid-April 2021, it infected 135,446,538 people in 223 countries or territorial areas, including almost three million deaths reported to the World Health Organization (WHO), so it was characterized as a pandemic[1]. In the same period, Brazil had more than 13 million cases of infection by SARS-CoV-2, with 353,000 deaths attributed to the disease[2].

The main symptoms of COVID-19 are fever, fatigue, and dry cough, which may progress to dyspnea or, in more severe cases, severe acute respiratory syndrome (SARS). To characterize the clinical spectrum, COVID-19 can be classified as mild (80%), severe (15%), or critical (5%), and the severity of the disease is associated with some underlying conditions[3].

With the detection and characterization of the etiological agent and its immunological consequences for the host, it was possible to identify the most frequent factors and conditions associated with morbidity, which enabled the development of protection and treatment protocols for the disease[4].

Different studies have found an association between SARS-CoV-2 infection and older age[5]. Elderly people present greater risk of hospitalization or death when diagnosed with COVID-19.

A meta-analysis that assessed about half a million patients with COVID-19 from different countries highlighted the effect of age on mortality of this disease, with relevance to ages above 50 years and, particularly, above 60 years[6]. For the U.S. Centers for Disease Control and Prevention (CDC), age-related risks increase significantly with aging and are not restricted to adults over 65 years of age. When compared to the age group from 5 to 17 years, the risk of death from COVID-19 is 45 times greater in adults aged 30 to 39 years and 8,700 times greater in elderly persons aged 85 years or over[7].

Several clinical conditions increase the risk of COVID-19 severity, such as cardiovascular diseases (CVD) and pulmonary diseases[7-9]. Data obtained from an assessment of 45,000 individuals in China showed a mortality rate of 0.9% in patients with COVID-19 without any underlying pathology, but this rate increased in patients with CVD (10.5%), diabetes mellitus (DM) (7.3%), or systemic arterial hypertension (SAH) (6.3%)[8]. According to the CDC, underlying clinical conditions that increase the risk of severity include: chronic kidney disease, chronic obstructive pulmonary disease (COPD), obesity, compromised immune system, severe heart conditions, sickle cell disease, type 2 DM, asthma, SAH, pregnancy, and neurological conditions such as dementia and cerebrovascular accident (CVA)[7].

Considering the high prevalence of these disorders worldwide, COVID-19 has caused major consequences. In addition, multimorbidity involves an even more complex interaction in the clinical management of patients with this disease[9].

Several biomarkers have also been reported as prognostic indicators and markers of the disease state, whether hematological, cardiac, hepatic or renal indicators[10-13].

In general, laboratory findings regarding SARS-CoV-2 infection indicate leukocytosis or leukopenia, lymphopenia and neutrophilia, all related to an unfavorable prognosis. Changes in blood clotting and reduced hemoglobin concentration are also present. Inflammatory biomarkers associated with severe COVID-19 include C-reactive protein (CRP), procalcitonin, D-dimer, erythrocyte sedimentation rate, serum ferritin, interleukin 6, and other cytokines. Specific heart, liver and kidney biomarkers are also associated with severe cases of the disease, such as creatine kinase (CK), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), urea, creatinine, cardiac troponin, and serum amyloid A protein[10-13].

It is understood that, through scientific cooperation, the dissemination of research data that show the behavior of individuals with the disease can help establish safe recommendations for the diagnosis, prevention and clinical management of SARS-CoV-2 infection. Such studies are crucial for monitoring serious and emerging situations, as they provide data to health professionals and bodies, allowing the characterization of clinical findings and associations with the morbidity and mortality profile. Monitoring affected patients can also contribute to the definition of differentiated approaches for clinical practice and surveillance actions and help define strategies that can be shared with other municipalities.

Then, considering the above, this study aimed to identify the sociodemographic and clinical characteristics associated with the clinical outcome of patients hospitalized with COVID-19 in a private service in a city in the State of São Paulo.

METHOD

This is a quantitative, descriptive, retrospective, correlational, single-center study.

Study site and population

Data were obtained from an electronic database, with the inclusion of information from patients who took a COVID-19 test in an emergency service of a private institution located in a city in the State of São Paulo, from July to December 2020. After analyzing all individuals seen during the study period, this assessment selected patients hospitalized in a ward or intensive care unit (ICU). Patients with incomplete data were excluded from the study.

Data collection instrument

The following information was extracted from the electronic database: sociodemographic data (gender, age, origin, admission place), clinical data (presence of comorbidities; imaging, hematological and biochemical exams; signs and symptoms; medications), and therapeutic data (COVID-19 therapy), as well as information about the clinical evolution or outcome, characterized as survival as indicated by hospital discharge, or lethality as indicated by death of hospitalized patient with a confirmed diagnosis of COVID-19, tested by reverse transcription polymerase chain reaction (RT-PCR). Comorbidities were defined according to the clinical records of underlying conditions presented by the patients that could increase the risk of severe COVID-19, such as old age, heart diseases, lung diseases, DM, dementia, and obesity[7].

The electronic database was created by the healthcare team based on the clinical data repository of patients (physical and electronic records) in order to assess the clinical evolution of patients with COVID-19 treated in the study site and support decisions to address SARS-CoV-2 infection. Based on patient information, the health team was able to monitor the clinical manifestations and evolution of patients and evaluate the results of therapeutic management to review drug and preventive behaviors, aiming to preserve patient health and safety. Such information allowed the identification of comorbidities and frequent severity factors among hospitalized patients with COVID-19 and better knowledge about the outcome following hospitalization.

Treatment protocol

The treatment, developed to standardize the management of patients with suspected or confirmed infection by SARS-CoV-2, was defined by health professionals based on recommendations from official bodies[3-4].

All professionals involved were trained to implement the protocol, which had objectives, detailed definitions, and a detailed algorithm for the therapeutic management indicated for adults, children and pregnant women, defined for phase I (until day 6 of symptoms) and phase II (days 7-10 of symptoms) of the disease.

Aspects were specified such as definition of flu-like syndrome, conditions and risk factors associated with complications of flu-like syndrome, clinical syndromes associated with COVID-19, interpretation of diagnostic tests, isolation precautions, possibilities for teleconsultation and telemonitoring.

In phase I, after the evaluation of the patient with flu-like syndrome who sought the care center, the patient was submitted to a treatment (with antipyretic, analgesic, cough suppressant/expectorant, and antiemetic drugs, whenever clinically indicated) and nasal and nasopharyngeal swab sampling was used for the RT-PCR molecular test. It was collected between day 3 and 6 of symptoms and the result and diagnosis were verified up to three hours after the exam. In phase II, the RT-PCR molecular test was requested to all individuals with flu-like syndrome or suspected COVID-19. In both phases, when the diagnosis of COVID-19 was confirmed, criteria were highlighted for supporting tests in the clinic, such as oximetry, blood count, blood coagulation test, LDH, inflammatory markers (PCR), renal function tests (plasma levels of urea and creatinine), and liver enzymes (plasma levels of AST, ALT, GGT), hypercoagulability marker (D-dimer). In phase II, a computed tomography (CT) scan of the chest was requested to patients with respiratory tract involvement.

Subsequently, if indicated and consented by the patient and/or guardian, a specific pharmacological treatment was provided (corticosteroid therapy, antibiotic therapy, anticoagulation for patients with elevated D-dimer level or worsening of respiratory symptoms). Antimalarial drugs were prescribed only for patients with an electrocardiogram (ECG) within the normal range and after clarification of the risks associated with the medication use. When used, ECG was performed at regular intervals to monitor the QTc interval. Teleconsultation and telemonitoring activities monitored the health status of patients. When hospitalization was indicated, data related to the admission place and outcome (survival or lethality) were recorded in the electronic database by a nurse from the study site.

Children and pregnant women had a specific protocol, with the therapeutic approach defined by pediatricians and obstetricians, respectively. For children with a confirmed diagnosis of COVID-19, antibiotic and antiparasitic drugs were prescribed with a dosage that was adequate for their weight and age. Pregnant women were treated with supportive therapies, and the use of specific therapeutic agents from the COVID-19 treatment protocol was guided by an individual assessment of risks and benefits. Any gestational age or puerperium up to two weeks after delivery (including miscarriage or fetal loss) was considered a warning for possible complications of the health condition. Both children and pregnant women were included in the telemonitoring actions.

Data analysis

Data stored in Excel spreadsheets were coded, exported and analyzed in IBM SPSS Statistics version 25 and R i386 v3.5.3. The association between variables was analyzed using the non-parametric Pearson's chi-square test and Fisher's exact test. A statistical significance level of 5% ($p<0.05$) was adopted for all analyses.

Ethical aspects

This study was approved by the Research Ethics Committee of the Nursing School in Ribeirão Preto, University of São Paulo, under CAAE 40889120.9.0000.5393.

RESULTS

This study included 2,515 patients with a diagnosis of COVID-19 confirmed by laboratory tests, treated between July and December 2020. Positive tests represented 28.4% of total 8,853 tests. The average positivity rate per month was 24.8%, with the highest rate in July (40%) and the lowest rate in November (10.4%).

Of the total study population, 117 patients (4.7%) were hospitalized. Figure 1 shows the distribution of hospitalized patients by month of hospitalization.

Table 1 shows the distribution of hospitalized patients according to sociodemographic and clinical variables.

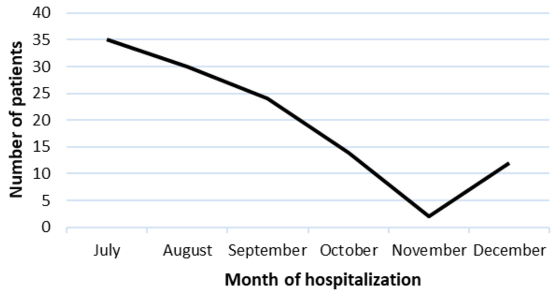

Figure 1. Distribution of hospitalized patients with diagnosis of COVID-19 (n=117), according to the month of hospitalization in 2020. Source: Developed by the authors.

Table 1. Distribution of hospitalized patients with diagnosis of COVID-19 (n=117) according to sociodemographic and clinical variables, July-December 2020.

Variable		n	%
Sex			
	Male	62	53.0
	Female	55	47.0
Age group			
	≤10	01	0.9
	11-20	01	0.9
	21-30	02	1.7
	31-40	09	7.7
	41-50	16	13.7
	51-60	22	18.8
	61-70	31	26.5
	71-80	18	15.4
	81-90	12	10.3
	>90	05	4.3
Frequent comorbidities			
	Arterial hypertension	65	55.6
	Diabetes mellitus	39	33.3
	Obesity	16	13.7
	Heart disease	14	12.0
	Chronic lung disease	10	8.5
	Cerebrovascular accident	08	6.8
	Alzheimer/dementia	08	6.8
	Dyslipidemia	08	6.8
	Hypothyroidism	06	5.1
Frequent severity factors			
	Oxygen saturation <96%	95	81.2
	Increased C-reactive protein	62	53.0
	>64 years	56	47.9
	Elevated D-dimer level	24	20.5
	Lymphopenia	20	17.1
	Thrombocytopenia	14	12.0
	Change in renal function	13	11.1
Place of hospitalization			
	Ward	95	81.2
	Intensive care unit	22	18.8
Outcome			
	Discharge	82	70.1
	Death	35	29.9

Source: Developed by the authors.

Change in renal function was determined by the results of serum urea and creatinine, i.e., values above 50 milligrams per deciliter (mg/dl) and 1.3 mg/dl, respectively, in patients without a history of renal complications.

Based on the database, the frequency of each comorbidity and severity factor was verified, adding up to obtain the total number of cases of each event (Tables 1 and 4). The test results helped predict the disease severity and assess the level of oxygen saturation (SaO2), reduction of immune response to the virus, associated bacterial infection, presence of lymphopenia, lymphocytosis, leukopenia, thrombocytopenia, lung and liver and renal failure, coagulation activation, among other alterations[10-13].

Table 2 shows the average minimum, maximum, median, mean, and standard deviation values of studied variables, according to the total number of COVID-19 hospitalizations.

Table 3 shows the associations between outcome, comorbidities, and severity factors in patients hospitalized with COVID-19. Of the total 2,515 infected patients, 35 (1.4%) died.

Table 4 shows the associations between clinical outcome and comorbidities or severity factors in patients hospitalized with COVID-19.

Table 2. Average minimum, maximum, median, mean, and standard deviation values of studied variables, according to the total number of COVID-19 hospitalizations, July-December 2020.

Total number of hospitalizations (n=117)	Comorbidity	Severity factor	Days of symptom	Days of hospitalization	Days in ICU	Days of hospitalization before ICU
Mean	1.8	4.1	8.0	8.7	8.9	5.3
Median	1.0	4.0	8.0	5.0	5.0	3.5
Minimum	0	0	01	01	01	01
Maximum	7	9	16	47	23	19
Standard deviation	1.4	2.2	3.7	8.9	7.6	4.9

Source: Developed by the authors.

Table 3. Associations between outcome and sociodemographic and clinical variables of patients hospitalized with COVID-19 (n=117), July-December 2020.

Variable		Discharge (n=82)		Death (n=35)		Total (n=117)		p*
		n	%	n	%	n	%	
Sex								
	Male	42	67.7	20	32.3	62	53.0	0.557
	Female	40	72.7	15	27.3	55	47.0	
Age group								
	≤10	01	100	0	-	01	0.9	
	11-20	01	100	0	-	01	0.9	
	21-30	02	100	0	-	02	1.7	
	31-40	09	100	0	-	09	7.7	
	41-50	14	87.5	02	12.5	16	13.7	
	51-60	16	86.4	03	13.6	19	16.2	
	61-70	18	58.1	13	41.9	31	26.5	0.002
	71-80	12	66.7	06	33.3	18	15.4	
	81-90	03	25.0	07	75.0	10	8.5	
	>90	03	60.0	02	40.0	05	4.3	
Comorbidity								
	Yes	64	66.7	32	33.3	96	82.1	0.115
	No	18	85.7	03	14.3	21	19.9	
Severity factor								
	Yes	80	69.2	35	30.4	115	98.2	
	No	02	100	0	-	02	1.8	1.00

*Fisher's exact test. Source: Developed by the authors.

Table 4. Associations between clinical outcome and main comorbidities or severity factors of patients hospitalized with COVID-19 (n=117), July-December 2020.

Variable			Discharge		Death		Total		p
			n	%	n	%	n	%	
Comorbidities									
	Arterial hypertension	Yes	46	70.8	19	29.2	65	100	0.857*
		No	36	69.2	16	30.8	52	100	
	Diabetes mellitus								
		Yes	24	61.5	15	38.5	39	100	0.153*
		No	58	74.4	20	25.6	78	100	
	Obesity								
		Yes	10	62.5	06	37.5	16	100	0.476*
		No	72	71.3	29	28.7	101	100	
	Heart disease								
		Yes	08	57.1	06	42.9	14	100	0.260*
		No	74	71.8	29	28.2	103	100	
	Chronic lung disease	Yes	08	80.0	02	20.0	10	100	0.721#
		No	74	69.2	33	30.8	107	100	
	Cerebrovascular accident	Yes	03	37.5	05	62.5	08	100	0.051#
		No	79	72.5	30	27.5	109	100	
	Dyslipidemia								
		Yes	04	50.0	04	50.0	08	100	0.237#
		No	78	71.6	31	28.4	109	100	
	Alzheimer/ dementia	Yes	03	37.5	05	62.5	08	100	0.222*
		No	79	72.5	30	27.5	109	100	
	Hypothyroidism								
		Yes	05	83.3	01	34.0	06	100	0.051#
		No	77	69.4	34	30.6	111	100	
Severity factors									
	Oxygen saturation <96%	Yes	65	68.4	30	31.6	95	100	0.414*
		No	17	77.3	05	22.7	22	100	
	↑ C-reactive protein	Yes	46	74.2	16	25.8	62	100	0.303*
		No	36	65.5	19	34.5	55	100	
	>64 years								
		Yes	30	56.3	26	46.4	56	100	<0.001*
		No	52	85.2	09	14.8	61	100	
	↑ D-dimer								
		Yes	18	75.0	06	25.0	24	100	0.555*
		No	64	78.8	29	31.2	93	100	
	Lymphopenia								
		Yes	15	75.0	05	28.0	20	100	0.598*
		No	67	69.1	30	30.9	97	100	
	Thrombocytopenia								
		Yes	07	50.0	07	28.0	14	100	0.080*
		No	75	72.8	50	27.2	103	100	
	Change in renal function	Yes	05	38.5	08	27.0	13	100	0.008*
		No	77	74.0	27	26.0	104	100	

*Chi-square test; #Fisher's exact test. Source: Developed by the authors.

DISCUSSION

This study showed that, among hospitalized patients diagnosed with COVID-19, the unfavorable clinical outcome, i.e., death, was significantly associated with the age group above 64 years and altered renal function – variables considered as risk factors for severe disease.

It also showed the positivity rate – the percentage of patients who tested positive for the virus over time – was high (28.4%) among the studied patients. This finding agrees with Brazilian data from the final months of 2020, when states like São Paulo, Bahia, Rio de Janeiro, Mato Grosso do Sul, and Rio Grande do Sul presented positivity rates of 25% to 50% for a few weeks. These high positivity rates may indicate uncontrolled epidemic or insufficient testing, when only critical patients or those seeking medical care are tested, without a wide network to measure the spread of the virus in the community. According to the WHO, a positivity rate of max. 5% for at least 14 days indicates the epidemic is under control[14-15].

However, considering the scarcity of diagnostic tests in developing countries, the real incidence of COVID-19 in Brazil may be underestimated. Monitoring the pandemic through metrics focused on the actual number of cases and deaths among the population involves a restriction – the ability of health systems to detect and confirm the cases and deaths caused by COVID-19[14]. In this context, Brazil is the 14th country in the world in number of tests performed and 120th among all countries considering the proportion of tests per number of inhabitants[16].

Most hospitalizations due to COVID-19 occurred in July 2020 (35 patients or 29.9% of all patients admitted). A gradual reduction was seen in hospitalization until November, when the lowest number of hospitalized patients was reported (1.7%). These results were similar to those observed during the evolution of the pandemic in the country, where the number of COVID-19 cases increased in March, reached its peak in July, and began to decrease from August to October, but in an irregular manner. Since then, this trend has reversed, with a more intense increase than in the 1st half of 2020, particularly in epidemiological week 46 in November[17-18].

These findings indicate the frequency of hospitalization among patients (4.7%) was lower than that reported by other authors[19], who reported around 80% of SARS-CoV-2 patients with mild or no symptoms, 20% requiring hospitalization, and around 5% requiring ICU admission. The low frequency of hospitalization found in our study may be related to lower lethality of the virus strain in the data collection period and/or may be the result of early identification of the condition and therapies for patient treatment (teleconsultation and telemonitoring, early identification of risk factors, supportive measures, symptomatic treatment, and specific pharmacological therapy), since all patients had health plans and were promptly assisted.

In Brazil, the number of hospitalizations and in-hospital mortality rates were higher in the North and Northeast regions when compared to the South and Southeast regions. One of the factors related to these findings was the difference in the number of hospital beds and ICU beds per capita in different locations. Contrasts in mortality data were consistent with regional inequalities in access to quality health care before the pandemic, indicating that COVID-19 disproportionately affects not only the most vulnerable individuals, but also the most fragile health systems[18].

Regarding the proportion of deaths among patients with a confirmed diagnosis of COVID-19, a 1.4% mortality rate was identified in the study population. This rate has varied significantly between countries since the pandemic started (0.1% to more than 25%)[17]. Factors that influence the different mortality rates include demographic characteristics, testing capacity, and different conditions of population access to health services. In September 2020, the mortality rate in Brazil was 3%; in April 2021, 2.7%, 2.5% in the study city, 3.2% in the State of São Paulo and 2.1% in the world[17].

Hospitalized patients were mostly male (53%), aged 61 to 70 years (26.5%).

Age is a marker of gradual accumulation of permanent damage over time and, consequently, it is highly associated with chronic diseases. Epidemiological and social environments enhance such association[20].

In this context, studies show SARS-CoV-2 lethality has been mostly associated with elderly patients and the presence of comorbidities that affect the immune system[21], with evidence showing individuals with underlying chronic diseases pose a higher risk of having severe COVID-19[20].

Likewise, data from 220 hospitalized and 311 non-hospitalized patients with COVID-19 from six hospitals and outpatient clinics in Atlanta, U.S., revealed that older age, male patients, black race, DM, lack of health insurance, smoking, and obesity were independently associated with hospitalization[22].

A retrospective analysis by Ranzani et al.[18] of the first 250,000 hospitalizations due to COVID-19 in Brazil from February 16 to August 15, 2020, reported mean age of 60 years, 119,657 (47%) of patients were under 60 years, and 143,521 (56%) were male. In-hospital mortality in patients under 60 years represented 31% in the Northeast region and 15% in the South region.

Among the study participants, most were admitted to the ward (for 8.7 days). However, 18.8% were directly sent to the ICU, where they remained for around nine days. The average duration of symptoms, before hospitalization, was eight days. A retrospective cohort study assessing 191 hospitalized patients in China reported the time between symptom onset and hospital admission ranged from 8 to 14 days (average time of 11 days) and the time between symptom onset and ICU admission ranged from 8 to 15 days (average time of 12 days)[19].

Ruíz-Quiñonez et al.[23] found shorter hospital stays due to COVID-19 (4.75±4.43 days). Macedo et al.[24] reported older age of hospitalized patients who progressed to death due to COVID-19 than hospitalized individuals who recovered from the disease (mean of 68.8 and 57.7 years, respectively). On average, the hospital stay for the group that progressed to death totaled 10.1 days, while recovered patients were hospitalized for 16.1 days. The period from diagnosis to outcome (death or recovery) was, on average, 17.2 days for those who had a fatal outcome and 24.7 days for recovered patients. These authors concluded that younger age and longer time from diagnosis to outcome were the variables associated with longer hospital stays.

The results found in this study showed that 29.9% of hospitalized patients died, with a statistically significant association between the outcome and the age group. Although most deaths occurred among male patients, no association was observed between sex and outcome. Considering the total number of participants, deaths occurred predominantly in the age group from 61 to 70 years (26.5%); however, it should be noted that 75% of hospitalized patients aged 81-90 years had a fatal outcome.

Macedo et al.[24], in a study conducted in Brazil, reported that 26.8% of hospitalized patients with COVID-19 died as a result of the disease. Similarly, an observational study in Mexico which analyzed information from 185 individuals with a confirmed diagnosis of COVID-19 who progressed to a fatal outcome showed mean age of 59.5 years and predominance of male patients (60.1%)[23]. Wenham et al.[25] also highlighted that around 59% of COVID-19-related deaths occurred in male patients.

In Brazil, until mid-September 2020, most people who tested positive for COVID-19 were aged 30 to 59 years and 73% of deaths were reported among people over 60 years[26-27].

Regarding the most frequent comorbidities, a high occurrence is observed of chronic disorders, such as SAH, DM, chronic lung disease, dementia, hypothyroidism, or risk factors for CVD, such as obesity and dyslipidemia, findings that were also reported by other researchers[7-8].

A study conducted in Iran compared 126 individuals diagnosed with SARS-CoV-2 infection and 252 symptomatic individuals but with negative diagnostic tests for the disease, and concluded the statistically significant risk factors for COVID-19 infection were: male individuals over 60 years of age, living in urban areas, married, with a history of contact with infected individuals, and presenting comorbidities[28].

Ranzani et al.[18] analyzed the profile of admitted patients diagnosed with COVID-19 in all Brazilian regions from February to August 2020, and 73% to 77% of them had one to two comorbidities.

In our study, although no association was found between the outcome and the presence of other illnesses, among the patients who progressed to death, 33% had comorbidities and 30.4% of them had one or more severity factors associated with the clinical condition.

Similarly, other authors identified the following comorbidities in individuals who died of SARS-CoV-2 infection: DM (60.63%), SAH (59.57%), obesity (43.61 %)[23], among others. In China, 15% of fatal patients were hypertensive and 9% had other CVDs[29]. In Brazil, based on a population of 3,896 hospitalized patients diagnosed with COVID-19, researchers identified the presence of comorbidities, particularly chronic kidney disease, was associated with an increased risk of mortality due to COVID-19[24].

Thus, underlying CVD seems to be associated with more severe clinical evolution of the disease and increased risk of death in patients with COVID-19. Also, SARS-CoV-2 infection can also cause myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism[30].

Regarding the high frequency of SAH found in this study, there is still no clear epidemiological evidence showing higher blood pressure is an aggravating factor of COVID-19[7]. However, hypertensive heart disease is the most common comorbidity in middle-aged and elderly adults, who also present a high frequency of fatal cases of COVID-19[31].

It is also reasonable to consider the high prevalence of arterial hypertension among patients with COVID-19 can be attributed to the vulnerability of elderly individuals to infection by SARS-CoV-2[32].

For some authors, the association between CVD, cardiovascular risk factors, acute respiratory distress syndrome (ARDS), and mortality due to COVID-19 seems to be related to the expression or function of the angiotensin-converting enzyme 2 (ACE2), which is part of the renin-angiotensin-aldosterone system (RAAS) and represents the main entry receptor for SARS-CoV-2[8]. In addition to ACE-2, dipeptidyl peptidase-4 (DPP4) also seems to act as a target for viral attachment[33].

Researchers also warn of a potential new pandemic of cardiovascular disease in the post-COVID-19 era if a more efficient therapeutic management is not developed for patients with a heart disease, with rigorous screening and identification of specific markers for morbidities that are more frequently associated with COVID -19[34].

Regarding the high frequency of DM reported in our study, in addition to the recognized association between severity of COVID-19 and DM, studies indicate that SARS-CoV-2 infection can also predispose individuals to hyperglycemia. In interactions with other risk factors, hyperglycemia can modulate immune and inflammatory responses, which may lead to disease aggravation and a fatal outcome[32].

According to the evidence, SARS-CoV-2 can cause an increase in the levels of blood inflammatory mediators, including lipopolysaccharide, inflammatory cytokines, and toxic metabolites. Modulation (increase or decrease) of natural killer cell activity and interferon-gamma (IFNγ) production may increase interstitial and/or vascular permeability for pro-inflammatory products. In addition, SARS-CoV-2 infection increases the production of reactive oxygen species (ROS). These effects lead to pulmonary fibrosis, acute lung injury, and ARDS. The production of ROS and viral activation of RAAS (via increased expression of angiotensin II) result in insulin resistance, hyperglycemia, and vascular endothelial damage, conditions that contribute to cardiovascular events, thromboembolism, and dissemination of intravascular coagulation. Infection also causes an increase in coagulation components, including fibrinogen and D-dimer, resulting in increases in blood viscosity and vascular endothelial damage, associated with cardiovascular alterations and coagulation disorders[34].

Regarding the frequency of dementia among patients hospitalized with COVID-19, people affected by dementia are more vulnerable, dependent and need more social support and health resources, and are more exposed to aggravating symptoms. Confinement and isolation due to the epidemic can deprive these individuals of their usual daily and therapeutic activities, contributing to severe neuropsychiatric symptoms and cognitive decline and morbidity[35].

Obese individuals should also be included as potentially susceptible to infection caused by the new coronavirus. Mechanisms by which obesity may influence adverse COVID-19 outcomes include chronic inflammation, compromised respiratory function and pulmonary perfusion, immune dysregulation, metabolic and vascular complications of obesity, and associated endocrine changes resulting from changes in the hypothalamic-pituitary hormonal axes, such as hypogonadism, hypothyroidism, and cortisol deficiency[36].

In addition, dyslipidemia is recognized as a risk factor linked with microvascular dysfunction in SAH, DM, and cardiovascular disorders, which help aggravate COVID-19. Cholesterol plays an essential role in the activation/dysregulation of the immune response and onset and pathogenesis of acute respiratory syndrome. It also enhances the endocytic entry of SARS-CoV-2 into target cells and may also be involved in endothelial damage in patients with COVID-19[37].

The main severity factors observed in the study participants were: low oxygen saturation (O_2), high CRP, age over 64 years, increased D-dimer, lymphopenia, thrombocytopenia, and alteration in renal function with an increase in serum levels of urea and creatinine. A significant association was also observed between the outcome and the variables of age over 64 years and alteration in renal function.

Relevant evidence shows that high CRP is one of the main prognostic markers of SARS-CoV-2 infection, as well as alteration in imaging tests (chest radiographs and computed tomography), low blood oxygen saturation, elevated neutrophil to lymphocyte ratio, and increased values of D-dimer and HDL cholesterol[12,36]. Also, patients who most likely progress to severe disease have higher baseline levels of inflammatory markers and D-dimer[38-39].

Regarding the changes in renal function and its association with the outcome, Gerotziafas et al.[37] and Pfister et al.[39] reported the association between kidney disease and in-hospital mortality in patients with COVID-19. The pathophysiology of COVID-19-induced kidney failure is not fully understood, but it results primarily from the host's immune response that leads to cytokine storm and aggressive inflammation. The mechanisms related to kidney injury suggest direct viral infection of glomerular and tubular cells and infection of indirect pathological mechanisms, with acute kidney injury as the most common complication.

One of the limitations of this study was that it was a single-center study, describing variables associated with the outcome of patients hospitalized with COVID-19 at the local level. However, by assessing the activity and outcome of COVID-19 in a specific region and context, this study highlights elements that can help local decision-making and the adoption of specific clinical interventions to mitigate the effects of this disease.

In addition, according to recommendations from the operational contingency plan[40] in force in Brazil, if associated with other data, contexts and population groups, these findings can contribute to a better understanding of the behavior of SARS-CoV-2 infection in a macroregion, supporting the development of preventive and therapeutic plans that covers the heterogeneity and specificity of the demands related to the new coronavirus in each territory.

CONCLUSIONS

This study identified an association between the COVID-19 outcome and variables of age over 64 years and changes in renal function with increased serum levels of urea and creatinine. The evaluation of how comorbidities and severity factors are related to the outcome is relevant for the disease management, favoring early identification of the conditions associated with SARS-CoV-2 infection and enabling a more effective therapeutic management.

Contribution of authors: Study conception and planning: VLD, VF, LMMA. Data collection, analysis and interpretation: VLD, VF, ECC, LMMA. Writing and revision of the manuscript: LMMA, ECC, SG, HBS.

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