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Predictive factors of hospitalization in an intensive care unit in patients with COVID-19: A case-control study

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ABSTRACT

Objective: The aim of the present study was to evaluate potential predictive factors for the aggravation of COVID-19 in patients hospitalized at a reference hospital in northeastern Brazil.

Methods: A non-paired case-control study was conducted with 235 patients hospitalized at a reference hospital in northeastern Brazil between March and April 2020. The case group was composed of individuals who required hospitalization in the ICU. The control group was composed of patients hospitalized due to COVID-19 who did not meet the criteria established in the institutional protocol for classification as "severe case of the disease" and therefore did not require intensive care.

Results: The case group was composed of 84 patients with a median age of 45 years (P_{25}-P_{75}: 36-59); 63.1% were men; 56.0% were less than 60 years of age; 76.2% had excess weight; 14.3% had a previous heart disease; 46.4% had hypertension; 11.9% had lung disease; and 67.1% took continuous-use medications. The median stay of severe cases in the ICU was positively correlated with weight and BMI only among female patients less than 60 years of age.

Conclusion: The logistic regression analysis revealed that age older than 60 years and a compromised cardiovascular system were independent predictive factors for the severity of COVID-19.

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KEYWORDS

COVID-19. Coronavirus. Intensive Care Unit. Risk Factors.

ABBREVIATIONS

COVID-19: the disease caused by SARS–COV-2.

WHO: The World Health Organization.

ICU: intensive care unit.

RT-PCR: reverse-transcription polymerase chain reaction.

RR: respiratory rate.

OR: odds ratio.

BMI: body mass index.

SPSS: Statistical Package for the Social Sciences.

ACE2: angiotensin converting enzyme 2.

INTRODUCTION

The first cases of COVID-19 (the disease caused by SARS–COV-2) were reported in China in December 2019[1,2]. The World Health Organization (WHO) announced the disease as a pandemic in March 2020[3].

Although most affected individuals present mild clinical manifestations of COVID-19 and have a good prognosis, some developed more severe forms, including pneumonia, pulmonary edema, severe acute respiratory syndrome, multiple organ failure, and death[4]. The transition from the mild to the severe form can occur quickly and prognostic factors for predicting which patients are at risk of developing the severe form continue to be exhaustively investigated[5]. The fact that there still is no effective treatment or vaccine for COVID-19 increases the challenge of designing prevention and control strategies for the disease[6].

Systematic reviews and meta-analyses involving populations from Asian, European, and North American countries show that an older age, the male sex, as well as preexisting heart disease, diabetes, and hypertension seem to be related to the development of more severe forms of the disease and the need for hospitalization in an intensive care unit (ICU)[5,7,8].

COVID-19 has a high incidence, low pathogenicity, and high mortality in severe cases of the disease. The syndemic focus of this infection has been the object of investigation by numerous researchers in the search for the identification of potential predictive factors that can modulate the development of the severe form of the disease[9].

OBJECTIVE

The aim of the present study was to assess potential predictive factors for the aggravation of COVID-19 in patients hospitalized at a reference hospital in northeastern Brazil.

METHODS

A non-paired case-control study was conducted involving patients ≥ 20 years of age hospitalized at a reference hospital in northeastern Brazil between March and April 2020. The diagnosis of COVID-19 was confirmed by the positive results of real-time reverse-transcription polymerase chain reaction (RT-PCR) of samples from nasal and pharyngeal swabs and clinical status. Pregnant women were excluded from the study. The criteria for hospitalization were acute infectious respiratory symptoms (with or without fever) as well as oxygen saturation < 95% on room air and/or respiratory rate (RR) ≥ 24 breaths per minute.

The case group was composed of individuals who required hospitalization in the ICU due to being classified with the severe form of the disease following the clinical protocol of the institution: patients requiring supplementary O_2 > 3 L/min, patients with RR greater than 24 breaths per minute and less than 30 breaths per minute associated with a risk factor, patients with RR greater than 30 breaths per minute independently of risk factors, patients with acute respiratory failure, sepsis, or septic shock, patients > 80 years of age (independently of risk factors) and patients > 65 years of age with an associated risk factor. The risk factors were age ≥ 65 years, chronic obstructive pulmonary disease, asthma, structural lung disease, cerebrovascular disease, heart disease, diabetes, arterial hypertension, chronic kidney disease, immunosuppression, pregnancy, morbid obesity, and chronic liver disease[10].

The control group was composed of patients hospitalized due to COVID-19 who did not meet the criteria established in the institutional protocol for classification as "severe case of the disease" and therefore did not require intensive care.

The sample size was calculated considering a 5% alpha error, 10% beta error (90% power), an odds ratio (OR) of 2.8, and exposure to systemic arterial hypertension of 28% among the controls. For such, the following formula was used:

$$n = \frac{\left\{ Z^{\beta} \sqrt{\left[\pi^{0}\left(1-\pi^{0}\right)\omega + \pi^{1}\left(1-\pi^{1}\right)\right]} + Z_{\alpha/2} \sqrt{\left[2\varpi\left(1-\varpi\right)\right]} \right\}^{2}}{\left(\pi^{1}-\pi^{0}\right)^{2}}$$

in which $\omega = \frac{\pi^{0}+\pi^{1}}{2}$ and $\pi^{1} = \frac{\pi^{0} OR}{1+\pi^{0}\left(OR-1\right)}$ [11]

Considering a proportion of one case to every two controls, the minimum sample was 70 cases and 140 controls, to which 10% was added to compensate for possible losses, leading to a minimum sample of 77 cases and 154 controls (total: 231 individuals).

Data were collected from patient charts and entered onto an electronic spreadsheet in Excel for Windows®. The following information was recorded:

Demographic data: sex and date of birth;

Anthropometric data: height and weight upon admission (self-reported by patient or measured by medical/nursing staff). In the absence of this information, the team of the Nutrition Service estimated weight using the Brazilian Silhouette Scale for Adults and Children[12] and height was estimated based on the height of the knee. The nutritional diagnosis based on the body mass index (BMI)[13] was categorized using the classification of the WHO[14];

Laboratory data: hemoglobin, leukogram, ultrasensitive C-reactive protein, lactate, and d-dimer upon admission;

Clinical data: patient and/or family history were taken upon admission, investigating a history of arterial hypertension, diabetes mellitus, heart disease, lung disease, neoplasms, and chronic kidney disease, as well as reported continuous-use medications (anti-hypertensive, oral glucose-lowering medication and/or insulin, etc.). Vital signs were also measured (oxygen saturation, respiratory rate, body temperature, and systolic/diastolic blood pressure). Clinical evolution during hospitalization was observed, such as the need for a bed in the ICU, the need for mechanical ventilation, and data on discharge or death (enabling the determination of the length of the hospital stay).

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 13.0 [SPSS Inc., Chicago, IL, USA]. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. As normal distribution was demonstrated, Pearson's correlation test (adjusted for age) was employed to investigate the correlation between the stay in the ICU and BMI. Bivariate analysis was performed between the dependent variable (need for intensive care) and the independent variables using Pearson's chi-square test with Yates' correction. The strength of the associations was evaluated using crude odds ratios (OR) and respective 95% confidence intervals.

A logistic regression model was created to examine independent predictive factors of the need for intensive care. For such, the *purposeful selection* method was used, with the inclusion of variables with a p-value < 0.20 in the bivariate analysis. Adjusted ORs and 95% confidence intervals were calculated. Variables with a p-value < 0.05 in the final model were considered significantly associated with the outcome. The goodness of fit of the model was determined using the Hosmer-Lemeshow test.

This study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki and all procedures involving the study participants were approved by the Research Ethics Committee of the *Real Hospital Português de Beneficência em Pernambuco/Instituto de Ensino e Pesquisa Alberto Ferreira Costa* (CAAE 33372920.2.0000.9030).

RESULTS

The case group was composed of 84 patients with severe cases of COVID-19 and the control group was composed of 151 patients with non-severe forms of the disease. Table 1 shows that the two groups were comparable with regards to age, BMI, oxygen saturation, respiratory rate, temperature, blood pressure, total and relative lymphocytes, C-reactive protein, lactate, leukocytes, and d-dimer.

In the case group, median age was 45 years (P_{25}-P_{75}: 36-59); 63.1% were men; 56.0% were less than 60 years of age; 76.2% had excess weight (BMI ≥ 25.0 kg/m²); 14.3% had a previous heart disease; 46.4% had hypertension; 11.9% had lung disease; and 67.1% took continuous-use medications, such as atenolol, metformin, losartan, etc. (Table 2).

The bivariate analysis revealed that the severity of COVID-19 in the present sample was modulated by a set of explanatory variables, especially the male sex, an older age, the occurrence of comorbidities, such as heart disease and systemic arterial hypertension, and the daily use of medications, which may be a proxy for chronic non-communicable diseases (Table 2). However, after the adjustment of potential confounding variables in the multivariate logistic regression analysis, only an older age (> 60 years) and a compromised cardiovascular vascular system were independent predictive factors for the severity of COVID-19 in patients hospitalized in this reference medical center (Table 3).

Table 1. Comparability of severe cases of COVID-19 and controls among patients hospitalized at reference hospital. Recife, northeast Brazil, 2020.

Variables	Cases n = 84 Md (P_{25} - P_{75})	Controls n = 151 Md (P_{25} - P_{75})	p*
Age (years)	45 (36-59)	46 (37-57)	0.624
BMI (kg/m^2)	29.2 ± 5.1	29.2 ± 5.6	0.980 †
Oxygen saturation (%)	96 (95-98)	97 (95-98)	0.299
Respiratory frequency (breaths per minute)	19 (18-22)	20 (18-21)	0.860
Temperature (ºC)	36.9 ± 1.0	36.7 ± 1.0	0.144 †
Systolic blood pressure (mmHg)	128 (120-136)	130 (120-140)	0.515
Diastolic blood pressure (mmHg)	80 (71-84)	80 (73-90)	0.100
Total lymphocytes (cells/mm^3)	1301 (956-1944)	1486 (1115-2149)	0.135
Relative lymphocytes (%)	26.5 (17.0-35.0)	25.0 (17.2-33.0)	0.538
C-reactive protein (mg/dL)	2.9 (1.0-6.4)	3.1 (1.0-9.3)	0.543
Lactate (mMol/L)	1.1 (0.8-1.6)	0.9 (0.6-1.6)	0.102
Leukocytes (cells/mm^3)	5835 (4292-6747)	6230 (4795-7495)	0.095
d-Dimer (ng/mL)	554 (372-786)	522 (361-821)	0.852

* Mann-Whitney U test † Student's t-test for unpaired data.

Table 2. Factors associated with severity of COVID-19 among patients hospitalized at reference hospital. Recife, northeast Brazil, 2020.

Variables	Cases n = 84 n (%)	Controls n = 151 n (%)	OR (95%CI)	p-value[a]
Sex				0.042
Male	53 (63.1)	73 (48.3)	1.83 (1.02-3.27)	
Female	31(36.9)	78 (51.7)	1.0	
Age group				0.000
≥ 60 years	37 (44.0)	16 (10.6)	6.64 (3.23-13.8)	
< 60 years	47 (56.0)	135 (89.4)	1.00	
Excess weight				0.332
Yes (BMI ≥ 25.0)	64 (76.2)	123 (81.5)	0.73 (0.36-1.46)	
No (BMI < 25.0)	20 (23.8)	28 (18.5)	1.00	
Obesity				0.908
Yes (BMI ≥ 30.0)	33 (39.3)	61 (40.4)	0.95 (0.53-1.71)	
No (BMI < 30.0)	51 (60.7)	90 (59.6)	1.0	
Obesity x ideal range				0.480
Obesity (BMI ≥ 30.0)	35 (62.5)	64 (69.6)	0.73 (0.34-1.56)	
Ideal range (BMI < 25.0)	21 (37.5)	28 (30.4)	1.0	
Heart disease				0.034
Yes	12 (14.3)	08 (4.0)	2.98 (1.07-8.41)	
No	72 (85.7)	143 (96.0)	1.0	
Hypertension				0.004
Yes	39 (46.4)	42 (27.8)	2.25 (1.24-4.08)	
No	45 (53.6)	109 (72.2)	1.0	
Lung disease				0.558
Yes	10 (11.9)	13 (8.6)	1.43 (0.55-3.70)	
No	74 (88.1)	138 (91.3)	1.0	
Continuous-use medications				0.004
Yes	51 (67.1)	55 (45.1)	2.49 (1.31-4.72)	
No	25 (32.9)	67 (54.9)	1.0	
Anemia*				0.927
Yes	11 (13.1)	19 (12.6)	1.05 (0.44-2.47)	
No	73 (86.9)	132 (87.4)	1.0	

*Criteria for anemia: hemoglobin <12.5g/dL for men and <11.5g/dL for women.

Table 3. Logistic regression for identification of independent predictors of COVID-19 severity among patients hospitalized at reference hospital. Recife, northeast Brazil, 2020.

Variables	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Sex		0.042		0.087
Male	1.83 (1.02-3.27)		1.04 (0.93-3.65)	
Female	1.0			
Age group		0.000		**0.000**
≥ 60 years	6.64 (3.23-13.8)		**7.34 (3.94-15.2)**	
< 60 years	1.0		1.0	
Heart disease		0.002		**0.000**
Yes	2.98 (1.07-8.41)		**3.02 (1.98-4.45)**	
No	1.0			
Hypertension		0.006		**0.021**
Yes	2.25 (1.24-4.08)		**2.86 (1.14-5.34)**	
No	1.0		1.0	
Continuous-use medication		0.004		0.108
Yes	2.49 (1.31-4.72)		1.84 (0.97-3.56)	
No	1.0		1.0	

The stay of the severe cases in the ICU tended to prolong *pari passu* with the increase in body weight and BMI (Table 4). However, this tendency was only found in female patients less than 60 years of age. Among men ≥ 60 years of age, a negative correlation was found between stay in the ICU and BMI. Moreover, male patients less than sixty years of age had a higher mean BMI (30.3 ± 5.2 kg/m^2) than those aged 60 years or older (28.1 ± 4.1 kg/m^2) (p = 0.037).

DISCUSSION

In the present sample, 35.7% of the hospitalized patients developed the severe form of the COVID-19 and required in-

Table 4. Correlation between stay in intensive care unit and sex adjusted for age and nutritional status among patients hospitalized with COVID-19 at reference hospital. Recife, northeast Brazil, 2020.

Length of stay in intensive care unit				
Variables	Men		Women	
	r*	p	r*	p
Age < 60 years				
BMI (kg/m^2)	-0.073	0.683	**0.567**	**0.004**
Age ≥ 60 years				
BMI (kg/m^2)	**-0.636**	**0.048**	0.340	0.509

* Spearman's correlation.

tensive care. This frequency is higher than that reported in studies conducted by Richardson et al[15], Teich et al[16] and Aidaoui et al[17] who respectively found that 14.2%, 27.8%, and 33.6% of patients required intensive care.

The most common report in the literature is the association between an older age and a greater risk of mortality due to COVID-19[7,8,18-20]. The explanation for this association is that aging has a negative impact on the immune response, together with an increase in the level of chronic inflammation. An inadequate immune system cannot effectively control the replication of the virus in the acute phase of infection and the occurrence of age-related chronic inflammation can increase the cytokine storm in later periods of the infection[8].

Regarding the need for intensive care, there are reports of a positive association with age[17] and no association with age[21]. The greater vulnerability of patients affected by COVID-19 to develop the severe form of the disease with the increase in age is a relevant finding, considering the accelerated aging of the population in the current demographic transition seen on a global scale. Due to the birth cohort effect, older people tend to experience important biological changes throughout life. Moreover, a reduction in immunological function is part of the aging process[8]. It is therefore plausible to suppose that the greater susceptibility to diseases in this age group in general is related to the peculiar characteristics of a generation that has been exposed to a greater number of risk factors, especially those of an endogenous nature, and may have indelibly incorporated biomarkers of risk (chronic inflammatory state, oxidative stress, nutritional disorders, etc.), as well as prolonged exposure to infectious and parasitic loads throughout life.

The high prevalence of comorbidities at the time of admission demonstrates the important role of chronic noncommunicable diseases in the epidemiological picture that characterizes the nosological profile of the population, especially in this age group. Aging is known to increase the proneness to cancer, type 2 diabetes mellitus, cardiovascular disease, lung disease, excess weight, and neurodegenerative diseases[22], all of which lead to a greater susceptibility to infection.

Regarding previous heart disease, which was an independent predictor for the aggravation of COVID-19 in the present sample, the prevalence among the cases was 14.3%. The literature reports higher frequencies of previous heart disease among patients hospitalized for COVID-19 that require intensive care. A study conducted in Morocco found a frequency of 28.9%[17] and a study conducted in the USA found a frequency of 31.8%[21].

Arterial hypertension was another independent predictive factor for the aggravation of COVID-19 among patients in the ICU at the reference hospital. The prevalence of hypertension in the case group was 46.4%. A frequency of 48.9% was reported in the study conducted in Morocco[17], whereas 70.4% was reported in the study conducted in the USA[21].

According to Askin et al[23], COVID-19 causes dysfunction of the myocardium in patients with previous cardiovascular comorbidities, increasing morbidity and mortality rates. SARS-CoV-2 binds to the receptor of human angiotensin converting enzyme 2 (ACE2), which is mainly expressed in the lungs, but can be released in the heart in cases of the excessive activation of the renin-angiotensin system, as occurs in hypertension, congestive heart failure, and atherosclerosis.

The exact mechanism of heart involvement in COVID-19 is not yet clear. However, myocardial involvement mediated by ACE2 is an important aspect. Other possible mechanisms are the cytokine storm induced by an imbalanced response among subtypes of T-helper cells and excess intracellular calcium, inducing apoptosis of hypoxic cardiomyocytes[23].

Excess weight is discussed as an important clinical condition to be considered in patients with COVID-19[1,21] but was not an independent predictor of the aggravation of the disease in the present sample. However, a positive correlation was found between BMI and length of stay in the ICU among women less than 60 years of age, as the median stay in the ICU was prolonged *pari passu* with the increase in body weight and BMI.

Luzi and Radaelli[24] report that obese individuals have altered innate and adaptive immune responses, characterized by a state of chronic, low-grade inflammation that causes the dysregulation of the immune response and contributes to the pathogenesis of complications related to obesity. The hypothesis is that obesity plays a role in the predisposition to severe complications of COVID-19 through several mechanisms, such as chronic systemic inflammation, related comorbidities (diabetes), and an increase in the secretion of IL-6. Another discussion is that excess fat can also lead to the presence of ectopic adipocytes in the alveolar interstitial space, which may suffer direct viral infection, thereby aggravating the inflammatory infiltrate and contributing to intense interstitial edema[25].

Some considerations should be added regarding the negative correlation between BMI and length of stay in the ICU among men aged 60 year or older. Brazil, which is a developing country, has a different morbidity and mortality profile among older people compared to developed countries[22]. Thus, the Manual of Nutritional Therapy in Specialized Hospital Care of the Brazilian Health Ministry[26] recommends that the classification of BMI for hospitalized individuals 60 years of age or older be in accordance with the reference figures of the Pan American Health Organization (2002): 23 to 28 kg/m^2 = adequate/ideal range; 28 to 30 kg/m^2 = overweight; and > 30 kg/m^2 = obesity. The mean BMI in this group was 28.1 ± 4.1 kg/m^2, which is close to the high end of the proposed ideal range. Therefore, a lower BMI, which is generally associated with mortality among Brazilian older adults[27], may have contributed to clinical complications that increased the length of stay in the ICU.

The present study has limitations that should be addressed. The findings were based on patient charts with data recorded by different health professionals. Some initial information, such as preexisting diseases and continuous-use medications, depended on the patient's memory. Most data on weight and height were either reported or estimated. When hospitalized, patients older than 80 years of age were admitted to the ICU independently of other risk factors. The period from March to April was the onset of cases in the city, with greater caution exercised on the part of the population regarding social distancing measures, especially among risk groups. These factors may have exerted an impact on the results.

CONCLUSION

An older age, heart disease and systemic arterial hypertension were the triad of independent predictive factors for the aggravation of COVID-19 in patients with a confirmed diagnosis of the disease hospitalized at a reference hospital center in the city of Recife in northeastern Brazil.

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