Mortality and associated factors in patients with COVID-19: cross-sectional study

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Abstract

The novel virus severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is highly virulent and causes coronavirus disease 2019 (COVID-19), resulting in high morbidity and mortality mainly associated with pulmonary complications. Because this virus is highly transmissible, it was quickly spread globally, resulting in COVID-19 being declared as a pandemic. This study aimed to analyze the prevalence of mortality and factors related to mortality due to COVID-19 in patients with severe acute respiratory syndrome (SARS) at a university hospital in the Central-West region of Brazil. This retrospective cross-sectional study was based on an analysis of the medical records of patients with SARS aged >18 years and admitted to an intensive care unit due to COVID-19 with the requirement of invasive mechanical ventilation. Hospital death was considered as an outcome variable in this study. Moreover, demographic and lifestyle-related variables as well as the therapeutic measures used during the hospital stay were recorded and correlated with the death outcome. After excluding 188 medical records, 397 were analyzed. Most participants were men (59.7%), and the mortality rate in patients with SARS due to COVID 19 was 46.1%. Multiple regression analysis indicated that the independent factors associated with mortality in patients with SARS due to COVID 19 were the age of >60 years (p = 0.000) and use of azithromycin (p = 0.012). The mortality rate in patients with SARS due to COVID 19 and mortality was associated with older age and use of azithromycin.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the infection called coronavirus disease 2019 (COVID-19) according to the World Health Organization, is one of the highly virulent β-coronaviruses that infects humans and causes acute respiratory failure (ARF) due to pneumonia, with high mortality rates[1,2]. In addition, SARS-CoV-2 presents a major challenge for healthcare systems across the world. This is mainly because critically ill patients with ARF have to be monitored in an intensive care unit (ICU) mainly under the support of invasive mechanical ventilation (IMV) [2–4].

The diagnosis of COVID-19 is based on a reverse transcriptase polymerase chain reaction test[5]. To date, the treatment of COVID-19 is undefined, and the therapies are aimed at controlling clinical manifestations and providing ventilator support. Notably, some drugs with therapeutic potential are emerging in the medical field[6].

Although many researchers have investigated about SARS-CoV-2,[1–4] it is still important to explore the factors associated with mortality in patients with COVID-19, including the influence of sociodemographic conditions and the presence of chronic diseases, lifestyle, and treatments. Therefore, this study aimed to analyze the prevalence and factors related to mortality in patients with severe acute respiratory syndrome

(SARS) due to COVID-19 requiring IMV. These data are important for adopting appropriate behavior in the hospital environment.

Methods

This is a cross-sectional observational study conducted at an ICU in the Central-West region of Brazil. The study was approved by the local Research Ethics Committee on February 26, 2021 (protocol number: 4.563.056/2021; Certificate of Presentation for Ethical Appraisal (CAAE) number: 43454621.2.0000.5077). Data collection was performed from March 12, 2021 to May 26, 2022.

Patients admitted to the ICU, diagnosed with SARS-CoV-2 infection, requiring IMV, older than 18 years, and of both sexes, were included in the study. Patients who had three or more incompletely analyzed variables in their medical records, who had no record of death outcome due to transfer to another institution, or who demonstrated unclear association between deaths and SARS-CoV-2 infection were excluded from the study.

Patients who had clinical dyspnea and required supplemental oxygen, and the ratio of partial arterial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) [?] 300 mmHg were considered as having ARF[7].

Data regarding sociodemographic characteristics, chronic diseases, lifestyle, treatment, and hospital death were collected from medical records. In-hospital death was considered an outcome or a dependent variable. The considered sociodemographic variables were sex (male or female) and age. The considered chronic disease variables were systemic arterial hypertension; diabetes mellitus (DM); hypothyroidism; hyperthyroidism; chronic obstructive pulmonary disease; cardiovascular disease (CVD); cerebrovascular disease; mental health-related disease; history of thrombosis; hepatitis A, B, and C; asthma; and liver failure. The considered lifestyle variables were smoking, alcohol consumption, and illicit drug use. The considered treatment variables were the use of the prone position during hospitalization and the use of drugs, such as dexamethasone, azithromycin, chloroquine, orhydroxychloroquine, and low-molecular-weight heparin (enoxaparin).

For the sample size calculation, expected prevalence (or rate) of death of 45% was used,[8] with an error margin of 5.0% and a 95% confidence interval (95% CI) for a population of 300,000 inhabitants residing in the city of Rio Verde, State of Goiás, Brazil, and its neighboring districts. Thus, the sample size required for this analysis (prevalence calculation) was found to be 380 patients.

All statistical analyses were performed using the Stata statistical package, version 16.0 (StataCorp LLC, College Station, TX, USA). The variables were presented as absolute numbers (n) and relative frequencies (%) with mean and standard deviation. Poisson's regression was used to calculate the prevalence ratio and 95% CI, and$p$ -values was obtained using the Wald test. Variables with ap -value of <0.20 in bivariate analysis were included in multiple hierarchical Poisson regression analyses, with robust variance based on a hierarchical model[9]. The independent variables in this hierarchical analysis were classified as follows: (I) demographic data (gender and age), (II) chronic diseases (DM and mental illness), (III) clinical features (pronation), and (IV) medication use (azithromycin and heparin). Statistical significance was established using a cutoff value of $p < 0.05$. Notably, the$p$ -value of 0.000 indicates that the relationship is statistically significant at the $\alpha = 0.05$ level.

Variables without statistical power; that is, variables that after the bivariate analysis presented n < 10 in any stratum, were excluded from the multiple regression analysis[10]. Additionally, the variables of hyperthyroidism, mental illness, asthma, liver failure, smoking, and use of chloroquine/hydroxychloroquine were excluded.

Results

Overall, 585 medical records were evaluated for eligibility in March 2021; of these, 188 were excluded (Fig. 1). Thus, 397 patients admitted to the ICU with SARS due to COVID-19 and in need of IMV participated in this study. Of these, 59.70% were men with a mean age of 61.04 ± 0.76 years (range 20–111 years). Of the patients aged >60 years, 62.17% were men and 37.83% were women.

The prevalence of death in individuals with SARS due to COVID-19 was 46.10% (63.93% in men and 36.07% in women). Data regarding the prevalence and association of in-hospital death in patients with SARS due to COVID-19 are presented in Table 1. The bivariate analysis indicated that in-hospital death in patients with SARS due to COVID-19 was associated with the age of >60 years (prevalence ratio [PR] = 1.61; 95% CI: 1.26–2.04, $p = 0.000$). In addition, not having a diagnosis of hyperthyroidism (PR = 0.46; 95% CI: 0.41–0.51, $p = 0.000$), asthma (PR = 0.46; 95% CI: 0.41–0.51,$p = 0.000$), or liver failure (PR = 0.46; 95% CI: 0.41–0.51,$p = 0.000$) and not being a smoker (PR = 0.61; 95% CI: 0.46–0.82, $p = 0.002$) were considered protective factors for mortality in individuals with SARS due to COVID-19.

Pronation at some point during hospitalization (PR = 1.30; 95% CI: 1.03–1.64, $p = 0.028$), use of azithromycin (RP = 1.36; 95% CI: 1.09–1.69, $p = 0.005$), and use of chloroquine or hydroxychloroquine (PR = 1.76; 95% CI: 1.121–2.77, $p = 0.014$) were associated with the mortality of patients hospitalized with SARS due to COVID-19.

The variables included in the multiple regression analysis are shown in Table 2. After the multiple regression analysis, the age of >60 years ($p = 0.000$) and use of azithromycin ($p = 0.012$) remained independently associated with the mortality of patients with SARS due to COVID-19.

Discussion

The main results of the present study indicated a high prevalence of death in individuals with SARS due to COVID-19 who required IMV. The mortality rate was higher in individuals aged >60 years who received azithromycin during SARS-CoV-2 infection.

The prevalence of death (46.1%) in individuals hospitalized with SARS due to COVID-19 was similar to that reported in other studies[2,8]. Notably, the patients included in the present study were critically ill and treated with IMV on admission to the ICU. These data are concerning and underscore that the high mortality due to COVID-19 in critically ill patients may be because of the continuous need for respiratory support and long stays in the ICU[2].

The findings of the present study confirm that the survival of critically ill patients with COVID-19 is particularly low in elderly men. Moreover, age of >60 years was associated with in-hospital death. A systematic review also stated that advanced age has been recognized as an important risk factor for COVID-19 mortality[11]. One explanation is that aging leads to impaired functioning of multiple body systems, including the immune system, which is a factor involved in the increased mortality due to COVID-19 in the elderly[11].

Although mortality was higher in men, no statistical significance was observed in the present study. Grasselli *et al.* found a relationship between the male sex and increased mortality in patients with COVID-19 admitted to ICUs[2]. In addition to higher mortality, another large study involving 3.1 millions of patients with COVID-19 reported that the male sex was associated with a higher ICU admission rate[12]. This phenomenon is attributed to the fact that women have a higher number of CD4+ T cells, a more robust cytotoxic activity of CD8+ T cells, and greater production of immunoglobulin by B cells than men, enabling them to produce a more efficient cellular and humoral response[12].

The use of azithromycin was also associated with in-hospital death. Azithromycin is an antibiotic with anti-inflammatory and antiviral properties, and it was thought to have activity against SARS-CoV-2[13]. However, based on different studies, a systematic review reported that azithromycin, along with other medications, including angiotensin-converting enzyme inhibitors, aspirin, colchicine, hydroxychloroquine, inhaled corticosteroids, intranasal corticosteroids, interferon beta, ivermectin, lopinavir-ritonavir, and vitamin C, has no important benefit on any important outcome for patients with COVID-19[14]. Based on the present study design, this association between azithromycin and death does not indicate causality.

Dexamethasone may be beneficial in patients with COVID-19, mainly in more severe forms with exacerbated inflammatory activity, because of its potential anti-inflammatory effect, which confers it the ability to decrease gene transcription of several proinflammatory cytokines, chemokines, and adhesion molecules

by inhibiting the generation and release of these mediators. However, dexamethasone may also prevent B-cell-mediated antibody production and reduce T-cell immune function, which may result in a higher plasma viral load and an increased risk of secondary infections[15]. Although the present study did not report an association of dexamethasone use with mortality, a randomized clinical trial in patients hospitalized with COVID-19 in the United Kingdom comparing the use of 6 mg dexamethasone once daily for 10 days to placebo reported reduced 28-day mortality rate in patients with COVID-19 receiving either IMV or oxygen therapy without IMV, with no impact on mild cases without respiratory support[16].

Based on the current evidence, low-dose systemic steroids may be considered for specific patients with COVID-19 who are critically ill or require supplemental oxygen. However, routine use of corticosteroids should be avoided, particularly in patients with mild symptoms or in the early stages of the disease unless indicated for another reason, such as those related to an individual's condition[17,18]. The retrospective nature of this study and lack of standardization of dose and duration of therapy may have contributed to the absence of any association of corticosteroid use with mortality in the present study. This is because any use of dexamethasone, whether during the ICU stay or earlier, was considered in this study.

The prone position contributes positively to the ventilation-perfusion ratio and to the recruitment of dependent lung segments, culminating in the opening of collapsed dependent alveoli and thereby providing better gas exchange and oxygenation. Among mechanically ventilated non-COVID-19 patients with severe acute respiratory distress syndrome, those who were ventilated in the prone position had a lower mortality rate.[19] The prone position can reduce the relative fraction of the pulmonary shunt by 30% compared with the supine group in patients with injured lungs[20]. A recent meta-analysis demonstrated that the prone position improved the PaO2/FiO2 ratio, with better SpO2 than the supine position, in patients with COVID-19[21]. Despite the aforementioned beneficial effects, the present study found an association between pronation and death, which may actually reflect the greater severity in patients who were pronated to improve ventilation and gas exchange. However, after the multiple regression analysis, pronation was not confirmed as an independent factor associated with mortality.

The limitations of this study include the observational cross-sectional design, which made it impossible to establish a causal relationship between the variables. In addition, the data collection considered a sample from a medium-sized city in the State of Goiás; therefore, generalization of the results to the rest of the Brazilian population must be done with caution. Variables that included previous lung disease had a low prevalence; therefore, it was impossible to establish an association with the outcome variable or to associate the use of drugs, such as chloroquine and hydroxychloroquine, with mortality. In addition, variables, such as the length of hospital stay, ventilation parameters, and laboratory tests, were not examined. The authors recommend examining these variables in future studies.

Conclusions

The authors conclude that individuals with SARS due to COVID-19 requiring IMV have high mortality. In addition, an association of mortality with an age of >60 years and the use of azithromycin was observed.

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Figure 1. Study conduction flowchart according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Table 1. Association between hospital death in patients with severe acute respiratory syndrome owing to COVID-19 and sociodemographic data, chronic diseases, lifestyle, and treatment (n = 397).

		Hospital death	**Hospital death**	
Variable	**Frequency n (%)**	**Prevalence n (%)**	**PR (CI 95%)**	p
Genre				0.119
Male	237(59,70)	117(63.93)	1.20(0.95-1.50)	
Feminine	160(40,30)	66(36.07)	1	
Age				**0.000**
20-59	167(42,07)	57(31.15)	1	
60 or more	230(57,93)	126(68.85)	1.61(1.26-2.04)	
Systemic arterial hypertension				0.228
No	184(46.46)	91(49.45)	1	
Yes	212(53.54)	92(43.40)	1.139(0.85-1.52)	
Diabetes mellitus				0.082
No	275(69,27)	64(34.97)	1	
Yes	122(30,73)	119(65.03)	1.21(0.98-1.50)	
Hypothyroidism				0.800
No	374(94,21)	173(94,54)	1,06(0,66-1,72)	
Yes	23(5,79)	10(5,46)	1	
Hyperthyroidism				**0,000**
No	396(99,75)	182(99,45)	0,46(0,41-0,51)	
Yes	1(0,25)	1(0,55)	1	
Chronic obstructive pulmonary disease				0,622
No	363(91,44)	166(90,71)	0,91(0,64-1,30)	
Yes	34(8,56)	17(9,29)	1	
Cardiovascular disease				0,546
No	356(89,67)	166(90,71)	1,12(0,77-1,64)	
Yes	41(10,33)	17(9,29)	1	
Cerebrovascular disease				0,595
No	377(94,96)	175(95,63)	1,16(0,67-2,00)	
Yes	20(5,04)	8(4,37)	1	
Mental health related illness				0,185
No	384(96,73)	175(95,63)	0,74(0,47-1,15)	
Yes	13(3,27)	8(4,37)	1	
Thrombosis history				-
Não	396(99,75)	183(100,00)	-	
Sim	1(0,25)	0(0,00)	-	
Hepatitis A				0,469
No	392(98,74)	180(98,36)	1,31(0,63- 2,69)	
Yes	5(1,26)	3(1,64)	1	
Hepatitis B				0,469
No	392(98,74	180(98,36)	1,31(0,63-2,70)	

		Hospital death	**Hospital death**	
Yes	5(1,26)	3(1,64)	1	
Hepatitis C				0,469
No	392(98,74)	180(98,36)	1,31(0,63-2,70)	
Yes	5(1,26)	3(1,64)	1	
Asthma				**0,000**
No	391(98,49)	179(97,81)	0,46(0,41-0,51)	
Yes (treating)	1(0,25)	1(0,55)	1	
Yes (cured)	5(1,26)	3(1,64)	0,59(0,29-1,23)	
Liver failure				**0,000**
No	390(98,24)	178(97,27)	0,46(0,41-0,51)	
Yes (treating)	1(0,25)	1(0,55)	1	
Yes (cured)	6(1,51)	4(2,19)	0,66(0,38-1,17)	
Smoking				**0,002**
No	369(92,95)	167(91,26)	0,61(0,46-0,82)	
Yes (smoker)	9(2,27)	2(1,09)	0,30(0,09-1,06)	
Yes (already smoked)	19(4,79)	14(7,65)	1	
Alcohol consumption				0,397
No	345(86,90)	162(88,52)	1,16(0,82-1,65)	
Yes	52(13,10)	21(11,48)	1	
Use of illicit drugs				0,294
No	388(97,73)	177(96,72)	,68(0,30-1,53)	
Yes (user)	3(0,76)	2(1,09)	1	
Yes (already used)	6(1,51)	4(2,19)	0,67(0,30-1,48)	
Pronation				**0,028**
No	154(38,99)	60(32,97)	1	
Yes	241(61,01)	122(67,03)	1,30(1,03-1,64)	
Dexamethasone use				0,861
No	79(19,95)	37(20,33)	1	
Yes	317(80,05)	145(79,67)	0,98(0,75-1,27)	
Use of Azithromycin				**0,005**
Não	207(52,41)	81(44,75)	1	
Sim	188(47,59)	100(55,25)	1,36(1,09-1,69)	
Use of chloroquine or hydroxychloroquine				**0,014**
Não	390(98,73)	117(97,79)	0,57(0,36-0,89)	
Sim	5(1,27)	4(2,21)	1	
Use of Heparin (Enoxaparin)				0,074
Não	68(17,17)	24(13,19)	1	
Sim	328(82,83)	158(86,81)	1,36(0,97-1,92)	

		Hospital death	**Hospital death**	
CI: confidence interval; PR: adjusted prevalence ratio. The Wald test was used to calculate all "p" values, $p < 0.05$ was considered statistically significant (**bold**). Variables with p < 0.20 were later analyzed by multiple hierarchical Poisson regression.	CI: confidence interval; PR: adjusted prevalence ratio. The Wald test was used to calculate all "p" values, $p < 0.05$ was considered statistically significant (**bold**). Variables with p < 0.20 were later analyzed by multiple hierarchical Poisson regression.	CI: confidence interval; PR: adjusted prevalence ratio. The Wald test was used to calculate all "p" values, $p < 0.05$ was considered statistically significant (**bold**). Variables with p < 0.20 were later analyzed by multiple hierarchical Poisson regression.	CI: confidence interval; PR: adjusted prevalence ratio. The Wald test was used to calculate all "p" values, $p < 0.05$ was considered statistically significant (**bold**). Variables with p < 0.20 were later analyzed by multiple hierarchical Poisson regression.	CI: confidence interval; PR: adjusted prevalence ratio. The Wald test was used to calculate all "p" values, $p < 0.05$ was considered statistically significant (**bold**). Variables with p < 0.20 were later analyzed by multiple hierarchical Poisson regression.

Table 2 . Multiple regression analysis of the association of in-hospital death and sociodemographic data, chronic diseases, and treatment in patients with severe acute respiratory syndrome due to COVID-19 (n = 397).

Variable
Genre
Male
Feminine
Age
20-59
60 or more
Diabetes mellitus
No
Yes
Pronation
No
Yes
Use of Azithromycin
No
Yes
Use of Heparin (Enoxaparin)
No
Yes
CI: confidence interval; PR: prevalence ratio. Wald's test was used to calculate all p-values. $p < 0.05$ was considered statist

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