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ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH DEATH IN HOSPITALIZED PATIENTS WITH SEVERE ACUTE RESPIRATORY SYNDROME BY COVID-19: A RETROSPECTIVE LONGITUDINAL STUDY IN A CITY IN SOUTHEASTERN BRAZIL

Giovanna Rotondo de Araújo[1], Thais Almeida Marques da Silva[2], Selma Costa de Sousa[1,3], Mariângela Carneiro[1,4], Juliana Maria Trindade Bezerra[1,5,6] and David Soeiro Barbosa[1]

ABSTRACT

The COVID-19 pandemic represents a challenge for health systems. Considering the importance of determining possible risk groups, this study aimed to describe the epidemiological profile and to evaluate the factors associated with death in hospitalized patients with Severe Acute Respiratory Syndrome caused by SARS-Cov-2 (COVID-19), in Contagem, Minas Gerais, during the year of 2020. A bivariate logistic regression was performed for each explanatory variable, followed by step-by-step backward selection. Only adjusted variables showing a significant association remained in the final model. This study demonstrates that the chances of death in hospitalized patients were higher in men; people aged 60 years or older; that presented respiratory distress as a symptom; that were obese or immunocompromised; that had cardiac, hepatic, renal, pulmonary or neurologic chronic diseases; and that required intensive care unit admission or invasive respiratory support. We conclude that COVID-19 represents an enormous challenge for health systems, demanding the need for specialized hospital services. Therefore, knowing the risk profile is a necessary tool to optimize treatment and to prevent worse outcomes.

KEY WORDS: Severe acute respiratory syndrome; coronavirus infection; advance health care planning; health correlates; risk factor; covid-19.

1. Universidade Federal de Minas Gerais, Departamento de Parasitologia, Programa de Pós-Graduação em Parasitologia, Belo Horizonte, Minas Gerais, Brazil.
2. Faculdade Santa Casa de Belo Horizonte, Programa de Pós-Graduação em Medicina – Biomedicina, Belo Horizonte, Minas Gerais, Brazil.
3. Secretaria Municipal de Saúde, Prefeitura Municipal de Contagem, Minas Gerais, Brazil.
4. Universidade Federal de Minas Gerais, Faculdade de Medicina, Programa de Pós-Graduação em Infectologia e Medicina Tropical, Belo Horizonte, Minas Gerais, Brazil.
5. Universidade Estadual do Maranhão, Programa de Pós-Graduação em Ciência Animal, São Luís, Maranhão, Brazil.
6. Universidade Estadual do Maranhão, Campus de Lago da Pedra, Curso de Licenciatura em Ciências Biológicas, Lago da Pedra, Maranhão, Brazil.

Giovanna Rotondo de Araújo ORCID: https://orcid.org/0000-0002-7513-5087; Thais Almeida Marques da Silva https://orcid.org/0000-0002-5042-2004; Selma Costa de Sousa ORCID: https://orcid.org/0000-0002-6200-9743; Mariângela Carneiro https://orcid.org/0000-0002-9390-7714; Juliana Maria Trindade Bezerra ORCID: https://0000-0001-9840-6217; David Soeiro Barbosa ORCID: https://0000-0002-5241-5940

Corresponding author: David Soeiro Barbosa. E-mail: davidsoeiro@gmail.com

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INTRODUCTION

The severe acute respiratory syndrome coronavirus (SARS-CoV), also known as the "2019 novel coronavirus", was identified for the first time in the bronchoalveolar lavage fluid of hospitalized patients with pneumonia in Wuhan, China (Tan et al., 2020). Coronaviruses (CoVs) were described in the 1960s and classified within the family Coronaviridae, the largest within the order Nidovirales. They are enveloped viruses with a single positive strand of RNA, whose spike (S) protein are responsible for their crown appearance (Woo et al., 2010; Ashour et al., 2020). The genetic proximity to the coronavirus responsible for the SARS-CoV outbreak in 2003, lead the new coronavirus to be officially recognized as SARS-CoV-2 in February 2020 and its disease as COVID-19 (WHO, 2020a).

Transmission occurs especially through droplets and aerosols released by infected people (Salian et al., 2021) and the severity of symptoms can range from mild symptoms of a common flu, diarrhea and pneumonia to multiple organ failure, respiratory failure, shock and death (Sofi et al., 2020).

When it was declared as a Public Health Emergency of International Concern (PHEIC), by the World Health Organization (WHO), on January 30, 2020, the infection had already accounted more than 7,000 cases and 170 deaths in the country of origin. It also had spread to more 18 countries, from which seven did not have patients with a travel history to China and three had already notified community transmission (WHO, 2020b). In Brazil, the first suspected case was reported on January 27, 2020. However, it was only in the last week of February that the first cases were laboratory confirmed, one in São Paulo (São Paulo) and another in Barra Mansa (Rio de Janeiro). Death registration began three weeks later, five of them in São Paulo and two in Rio de Janeiro (Fiocruz, 2020a; Brasil, 2020).

Along with the first death notifications, new cases were reported in other metropolitan areas around the country, including all State capitals, except for São Luís (Maranhão), Cuiabá (Mato Grosso), Macapá (Amapá), Boa Vista (Roraima) and Porto Velho (Rondônia). Internalization trends from the metropolises could also be observed, with a growing concern due to the availability and ability of health services to attend the number of patients in need of specialized care, such as Intensive Care Unit (ICU) beds and respiratory support (Fiocruz, 2020a; Fiocruz, 2020b).

According to the epidemiological bulletin published on January 1, 2021, the State of Minas Gerais, located in the southeast region of the country, had already reported more than 500,000 confirmed cases and 12,000 deaths, while other 40 thousand cases were still under investigation (SES/ Minas Gerais, 2021). The municipality of Contagem, located in the Metropolitan Region of the State's capital Belo Horizonte, is the third most populous in the State (IBGE, 2020) and, during the beginning of the notifications in March

2020, it had only 21 Intensive Care Units (ICU) and 30 ward beds in the public network capable of caring for patients with SARS-CoV-2.

Considering the importance of determining possible risk groups, this study aimed to describe the epidemiological profile and to evaluate the factors associated with death in hospitalized patients caused by SARS-Cov-2 (COVID-19), in Contagem, Minas Gerais, during the year of 2020.

MATERIAL AND METHODS

Ethical aspects

This study has been approved by the Ethics Committee in Research of the *Universidade Federal de Minas Gerais* (CAAE 46251021.6.0000.5149) and it was carried out in accordance with the Resolution of the National Health Council (CNS) number 466/2012, of December 12, 2012 (CNS, 2012), which provides the guidelines and regulatory standards for research involving human beings.

Study area

The municipality of Contagem is part of the polarizing nucleus of urban and economic activities, and the health regional of the Metropolitan Region of Belo Horizonte, capital of Minas Gerais (SMEC/ Contagem, 2009; IBGE, 2020).

Located in the central region of the State, the municipality has an area of 194,746 km² and a population estimated of 668,949 inhabitants in 2020 by the Brazilian Institute of Geography and Statistics (IBGE). The administrative division has eight regionals: Sede, Eldorado, Riacho, Industrial, Ressaca, Nacional, Petrolândia e Vargem das Flores (SMEC/ Contagem, 2009; IBGE, 2020).

The services related to the Municipal Health Department constitute four Care Centers Psychosocial Center (CAPS), a Center for Specialized Consultations, a Reference Center for Health in the Worker (CEREST), 16 District Pharmacies, a Municipal Hospital, a Municipal Maternity, four Emergency Care Units (UPA), 23 Basic Health Units (UBS), ten Oral Health Teams, 87 Family Health Teams (ESF) and a low and medium complexity emergency room (SMS/ Contagem, 2023).

Study design and data source

A retrospective longitudinal study was carried out through SARS-COVID-19 databases made available by the Municipal Health Department of Contagem, Minas Gerais, in August 2021.

Descriptive analysis of the sociodemographic profile of patients

The annual incidence per 100,000 inhabitants was calculated according to Gordis (2017) and the lethality was calculated based on the number of deaths over cases. The total number of patients and their relative percentage were considered for the following variables: sex, age group, self-declared race, week of onset of symptoms, symptoms (fever, cough, sore throat, dyspnea, respiratory distress, low oxygen saturation, diarrhea, vomiting, abdominal pain, fatigue, and loss of smell or taste), existence of comorbidities [puerperal; patients with cardiac, hematological, hepatic, renal, pulmonary (added to asthma) or neurological chronic diseases; trisomy 21; obesity; diabetes; and immunosuppression], and the necessity of ICU accommodation or respiratory support. Descriptive analysis was performed using Excel software for Microsoft 365 version 2109 (CA, USA).

Statistical analysis of death associated factors

A preliminary analysis of the relationship between the independent variables and the response variable (hospital discharge × death from SARS-COVID-19) was done by using contingency tables.

To verify which were the possible associations, a bivariate logistic regression was performed for each explanatory variable, being the ones with more than two categories transformed into dummy variables. Aiming to avoid selection bias, and to allow better adjustment of the model to COVID data, the category "unknown" was maintained for variables for which information was missing. As a result, variables that presented $p < 0.30$ in the bivariate analysis were selected to compose the initial multivariable logistic model. The collinearity between the variables was tested and the Odds Ratio (OR) was used as a measure of association.

A step-by-step backward selection procedure was performed to discard the variables that, adjusted in relation to the others, did not present a significance level of $p < 0.05$, and to produce the final multivariable logistic regression models. Only adjusted variables showing a significant association ($p < 0.05$) with the occurrence of death from COVID-19 remained in the final model. The strength of association was determined by OR at a 95% confidence interval.

The likelihood ratio test was used to define the final models and the performance was evaluated by the area under the ROC curve.

RESULTS

In 2020, 2,288 residents of Contagem were hospitalized after developing Severe Acute Respiratory Syndrome by COVID-19. Considering the estimated total population for 2020 of 668,949 inhabitants (IBGE, 2020), an annual incidence of 342.03 cases per 100,000 inhabitants of the municipality was estimated. The number of confirmed deaths among hospitalized patients, excluding the 153 whose case evolution could not be confirmed, was 651, reaching a case fatality rate of 28.5%.

Considering the epidemiological week (EW) of onset of symptoms, EW19 to EW36 stood out as the peak of incidence, comprising the months from May to August. The characteristics of patients with SARS-COVID-19 during hospitalization and outcomes are summarized in Table 1. Regarding sociodemographic characteristics, males were predominant, with 53.0% of notifications, as well as people self-declared brown (46.0%) and older than 60 years old (56.7%).

Table 1. Characteristics of patients with SARS-COVID-19 during hospitalization and outcomes.

	Total	Outcome	
		Hospital Discharge	Cure
Characteristics	n (%)	n (%)	n (%)
Sex			
Male	1,127 (52.9)	376 (57.8)	751 (50.8)
Female	1,002 (47.1)	275 (42.2)	727 (49.2)
Age group			
≥ 60	1,207 (56.7)	498 (76.5)	709 (48.0)
< 60	922 (43.3)	153 (23.5)	769 (52.0)
Self-declared race			
White	502 (23.6)	241 (37.0)	261 (17.7)
Black	177 (8.3)	97 (14.9)	80 (5.4)
Brown	964 (45.3)	293 (45.0)	671 (45.4)
Yellow	7 (0.3)	0 (0.0)	7 (0.5)
Missing	479 (22.5)	20 (3.1)	459 (31.1)
Symptoms			
Fever			

Yes	1,120 (52.6)	310 (47.6)	810 (54.8)
No	754 (35.0)	218 (33.5)	527 (35.7)
Missing	264 (12.4)	123 (18.9)	141 (9.5)
Cough			
Yes	1,543 (72.5)	437 (67.1)	1,106 (74.8)
No	419 (19.7)	134 (20.6)	285 (19.3)
Missing	167 (7.8)	80 (12.3)	87 (5.9)
Sore throat			
Yes	283 (13.3)	64 (9.8)	219 (14.8)
No	1,382 (64.9)	390 (59.9)	992 (67.1)
Missing	464 (21.8)	197 (30.3)	267 (18.1)
Dyspnea			
Yes	1,542 (72.4)	497 (76.3)	1,045 (70.7)
No	432 (20.3)	101 (15.5)	331 (22.4)
Missing	155 (7.3)	53 (8.1)	102 (6.9)
Respiratory distress			
Yes	1,161 (54.5)	416 (63.9)	745 (50.4)
No	721 (33.9)	151 (23.2)	570 (38.6)
Missing	247 (11.6)	84 (12.9)	163 (11.0)
Low oxygen saturation			
Yes	1,431 (67.2)	479 (73.6)	952 (64.4)
No	496 (23.9)	98 (15.1)	398 (26.9)
Missing	202 (9.5)	74 (11.4)	128 (8.7)
Diarrhea			
Yes	249 (11.7)	61 (9.4)	188 (12.7)
No	1,417 (66.6)	395 (60.7)	1,022 (69.2)
Missing	463 (21.8)	195 (30.0)	268 (18.1)
Vomiting			
Yes	200 (9.4)	57 (8.8)	143 (9.7)
No	1,460 (68.6)	403 (61.9)	1,057 (71.5)
Missing	469 (22.0)	191 (29.3)	278 (18.8)
Abdominal pain			
Yes	70 (3.3)	20 (3.1)	50 (3.4)
No	1,064 (50.0)	281 (43.2)	783 (53.0)

Missing	995 (46.7)	350 (53.8)	645 (43.6)
Fatigue			
Yes	299 (14.0)	90 (13.8)	209 (14.1)
No	870 (40.9)	225 (34.6)	645 (43.6)
Missing	960 (45.1)	336 (51.6)	624 (42.2)
Loss of smell or taste			
Yes	137 (6.4)	30 (4.6)	107 (7.2)
No	1,013 (47.6)	277 (42.6)	736 (49.8)
Missing	979 (46.0)	344 (52.8)	635 (43.0)
Comorbidities			
Heart disease			
Yes	838 (39.4)	363 (55.8)	475 (32.1)
No	494 (23.2)	115 (17.7)	379 (25.6)
Missing	797 (37.4)	173 (26.6)	624 (42.2)
Hematological disease			
Yes	21 (1.0)	8 (1.2)	13 (0.9)
No	1,070 (50.3)	334 (51.3)	736 (49.8)
Missing	1,038 (48.8)	309 (47.5)	729 (49.3)
Hepatic disease			
Yes	24 (1.1)	16 (2.5)	8 (0.5)
No	1,058 (49.7)	324 (49.8)	734 (49.7)
Missing	1,047 (49.2)	311 (47.8)	736 (49.8)
Renal disease			
Yes	124 (5.8)	79 (12.1)	45 (3.0)
No	990 (46.5)	288 (44.3)	702 (47.5)
Missing	1,015 (47.7)	284 (43.6)	731 (49.5)
Pulmonary disease			
Yes	226 (10.7)	98 (15.1)	128 (8.7)
No	913 (42.9)	274 (42.1)	639 (43.2)
Missing	990 (46.5)	279 (42.8)	711 (48.1)
Neurological disease			
Yes	119 (5.6)	78 (12.0)	41 (2.8)
No	1,000 (47.0)	285 (43.8)	715 (48.4)
Missing	1,010 (47.4)	288 (44.2)	722 (48.9)

Trisomy 21			
Yes	7 (0.3)	0 (0.0)	7 (0.5)
No	1,077 (50.6)	340 (52.2)	737 (49.8)
Missing	1,045 (49.1)	311 (47.8)	734 (49.7)
Obesity			
Yes	168 (7.9)	71 (10.9)	97 (6.6)
No	949 (44.6)	288 (44.2)	661 (44.7)
Missing	1,012 (47.5)	292 (44.9)	720 (48.7)
Diabetes			
Yes	581 (27.3)	238 (36.6)	343 (23.2)
No	666 (31.3)	188 (28.9)	478 (32.3)
Missing	882 (41.4)	225 (34.6)	657 (44.5)
Immunosuppression			
Yes	78 (3.7)	43 (6.6)	35 (2.4)
No	1,014 (47.6)	302 (46.4)	712 (48.2)
Missing	1,037 (48.7)	306 (47.0)	731 (49.5)
ICU			
Yes	628 (29.5)	399 (61.3)	229 (15.5)
No	1,098 (51.6)	182 (28.0)	916 (62.0)
Missing	403 (18.9)	70 (10.8)	333 (22.5)
Respiratory support			
Invasive	338 (15.9)	276 (42.4)	62 (4.2)
No invasive	818 (38.4)	184 (28.3)	634 (42.9)
No	423 (19.9)	74 (11.4)	349 (23.6)
Missing	550 (25.8)	117 (18.0)	433 (29.3)

n = number of patients; % = percentage, ICU = Intensive Care Unit.

It was observed that sex, age group, self-declared race, symptoms of cough, sore throat, dyspnea, respiratory distress, low oxygen saturation, diarrhea, fatigue, smell and taste loss, existence of comorbidities (patients with cardiac, hepatic, renal, pulmonary or neurological chronic diseases; obesity; and immunosuppression), and the necessity of ICU accommodation or invasive respiratory support presented a significant p-value in the univariate logistic regression analysis.

The epidemiological variables associated (p < 0.05 and 95% CI) with death from SARS-COVID-19 in the final multivariable model (Table 2) were male (OR: 1.3; 95% CI 1.0-1.6) and age older than 60 years (OR: 3.2; 95% CI 1.0-1.6). The associated symptom was respiratory distress (OR: 1.5; 95% CI 1.1-2.0). The associated comorbidities were obesity (OR: 1.7; 95% CI 1.0-2.8), immunosuppression (OR: 3.5; 95% CI 1.8-6.5), having cardiac (OR: 1.5; 95% CI: 1.1-2.2), hepatic (OR: 4.4; 95% CI 1.2-15.0), renal (OR: 2.8; 95% CI 1.6 -4.8), neurological (OR: 3.6; 95% CI 2.1-6.2), or pulmonary disease and asthma together (OR: 1.6; 95% CI 1.6-2.4). And the associated outcomes were requiring admission to an intensive care unit (OR: 3.8; 95% CI 2.8-5.0) and invasive respiratory support (OR: 6.9; 95% CI 4.3-10.8). The area under the ROC curve from the post-test assessment of adequacy of the multivariable logistic regression model was 0.8564.

Table 2. Factors associated with death for SARS-COVID-19 patients.

	Bivariate analysis			Multivariate analysis		
Variable	OR	95%CI	p	OR	95%CI	p
Male	1.3	1.1-1.6	0.003	1.3	1.0-1.7	0.026
≥ 60 years old	3.5	2.9-4. 4	0.000	3.2	2.5-4.2	0.000
Obesity	1. 7	1.2-2.4	0.002	1.8	1.1-2.9	0.023
Respiratory distress	2.1	1.7-2.6	0.000	1.5	1.2-2.0	0.003
Immunosuppression	2.9	1.8- 4.6	0.000	3.5	1.9-6.5	0.000
Cardiac disease	2.5	2.0-3.2	0.000	1.6	1.4-2.2	0.006
Hepatic disease	4.5	1.9-10.7	0.001	4.4	1.3-15.1	0.017
Renal disease	4.3	2.9-6.3	0.000	2.8	1.6-4.8	0.000
Neurological disease	4.8	3.2-7.1	0.000	3.7	2.1-6.3	0.000
Pulmonary disease + asthma	1. 8	1.3- 2.4	0.000	1.6	1.1-2.5	0.025
ICU	8.8	7.0-11.0	0.000	3.8	2.9-5.1	0.000
Invasive respiratory support	21.0	14.5-30.5	0.000	6.9	4.4-10.8	0.000

OR = Odds Ratio; 95% CI = 95% confidence interval; p = p value, ICU = Intensive Care Unit.

DISCUSSION

The clinical form of COVID-19 presents itself in an extensive range of symptoms (Sofi et al., 2020; WHO, 2022), being the Severe Acute Respiratory Syndrome an acute form with devastating effects worldwide. Brazil was largely affected by the disease, with high trends of lethality and a considerable burden on its hospital systems (Silva et al., 2022; Zeiser et al., 2022). This study evaluated the epidemiological aspects and factors associated to death in hospitalized patients in the municipality of Contagem, the third most populous in the State of Minas Gerais.

Despite the first official notification in the country being dated only on January 27, 2020 (Brasil, 2020), the first EW of the year already had two patients showing symptoms in Contagem, reaching seven patients by the end of the EW9.

Being the group with most notifications, men also had a higher OR of death when compared to women. This relationship is consistent with other findings in the literature for Brazil (Soares et al., 2020; Baggio et al., 2021; Prado et al., 2021; Silva et al., 2021; Colnago et al., 2022) and worldwide (Grasselli et al., 2020; Hesni et al., 2022; Ombajo et al., 2022). The possible explanation is that coronaviruses invade host cells by binding to angiotensin-converting enzymes 2 (ACE2), which are transmembrane proteins present in greater amounts in male circulating plasma cells than in female ones (Soro-Paavonen et al., 2012; Patel et al., 2013; Roberts et al., 2013; Grasselli et al., 2020).

Age is frequently reported as a prognostic factor associated with death from SARS-COVID-19 in the literature of Minas Gerais (Silva et al., 2022), Brazil (Soares et al., 2020; Baggio et al., 2021; Prado et al., 2021; Silva et al., 2021; Colnago et al., 2022), and worldwide (Grasselli et al., 2020; Kim et al., 2021; Hesni et al., 2022; Ombajo et al., 2022; Sato et al., 2022). Our results reinforce that the chance of death increases with the age of the patient. Several factors could influence this relationship, including longer hospitalization and associated risks, immunosenescence - a gradual decline in immune function capable of hindering immune defense mechanisms, as well as other social and environmental factors (Chen et al., 2021; Silva et al., 2022). The presence of comorbidities and their influence on the disease's outcome is largely discussed in literature and it may be linked with the high mortality in elderly patients, since the increased rate of comorbidities on this age group can extend immune system impairment and worsen COVID-19 outcomes (Bartleson et al., 2021; Chen et al., 2021; Sato et al., 2022).

COVID-19 has a wide range of symptoms, starting from the most common that are fever, cough, fatigue/ tiredness, and taste or smell loss; to less common, such as sore throat, headache, aches and pains, diarrhea, rash on skin and red or irritated eyes; and finally, to the most serious symptoms of difficulty breathing, shortness of breath, speech or mobility loss, confusion and chest pain (WHO, 2022). Despite all the symptoms analyzed in this study, only respiratory distress made it to the final multivariate model. At the State of Acre, northern Brazil, symptoms of sore throat and headache were negatively associated with death (Prado et al., 2021). This outcome is not unexpected, since most of the cited symptoms are related to mild cases and are unspecified, therefore, could not act as death predictors of severe cases.

Many studies have previously demonstrated that the presence of one or more chronic diseases is a risk factor associated with COVID-19 mortality in Brazil (Soares et al., 2020; Baggio et al., 2021; Prado et al., 2021; Silva et al., 2021; Colnago et al., 2022), and worldwide (Grasselli et al., 2020; Kim et al., 2021; Hesni et al., 2022; Ombajo et al., 2022; Sato et al., 2022). Obesity (Soares et al., 2020; Baggio et al., 2021; Sato et al., 2022); cardiac (Soares et al., 2020; Baggio et al., 2021; Prado et al., 2021; Silva et al., 2021), hepatic (Kim et al., 2021), renal (Soares et al., 2020; Baggio et al., 2021; Ombajo et al., 2022; Sato et al., 2022), pulmonary (Grasselli et al., 2020; Soares et al., 2020; Baggio et al., 2021; Kim et al., 2021; Silva et al., 2021; Sato et al., 2022), and neurologic chronic diseases (Silva et al., 2021); and immunocompromising (Baek et al., 2021) were significant comorbidities in this study and they may also be found in COVID-19 risk associations in other populations. Other comorbidities that were significant in the univariate analysis, and in other studies in the literature, but did not make to the final multivariate model were diabetes (Soares et al., 2020; Baggio et al., 2021; Kim et al., 2021; Prado et al., 2021; Silva et al., 2021; Ombajo et al., 2022) and hypertension (Baggio et al., 2021; Kim et al., 2021).

Despite pneumonia being frequently present in COVID-19 severe patients, adverse effects can occur in other organs and tissues, since all structures that express ACE2 are susceptible to infection (Lopes-Pacheco et al., 2021). Cardiovascular diseases, hypertension and hyperglycemia due to diabetes have a role on increasing ACE2 expression, making the patients more susceptible (Soro-Paavonen et al., 2012; Roberts et al., 2013; Drucker, 2021). The obesity related and sex-dependent altered expression of ACE2 had previously been reported in mice's lungs, trachea, and esophagus (Sarver & Wong, 2021) and could explain the worst outcome in the SARS-CoV lung injury (Kuba et al., 2005).

The admission to the ICU and the use of invasive respiratory support increased the chance of death in this study and in others (Hesni et al., 2022; Ng et al., 2022), probably due to the already deteriorated health status of the patients.

Similar results were also found nationally during the Omicron wave in 2021 and 2022, with males, 60 years or older and patients with comorbidities being more likely to die (Colnago et al., 2022). However, disease's outcomes are influenced not only by viruses' strains, but also by health individualities and social context, and Silva et al., (2022) did not find that sex and chronic diseases were significant death predictors in their study in Uberaba, Minas Gerais. Conversely, the study found a 40% increase in the odd of death for every 10 years of life, and the high mortality among the elderly could have hindered the mortality related to sex and chronic diseases (Silva et al., 2022). Therefore, local studies focusing on specific populations are important for better health management and public policies designing.

The investigation of risk factors in Contagem, Minas Gerais, had the considerable large amount of missing data as the major limitation. Despite having had access to the municipality's database, excluded any individual information that could lead to patient identification, missing data may have impacted the results and introduced bias information. In order to avoid bias, the missing data was transformed into a valid category in the univariate and multivariate models, and it was not statistically significant ($p > 0,05$) in all variables that made to the final multivariate model, improving the fit of the final model to the data. Thus, this study contains information on patients hospitalized in 2020, the frequency and distribution of the studied variables could have changed as additional data became available and new COVID-19 strains reached the municipality.

In conclusion, this study demonstrates that the chances of death in hospitalized patients are higher in men; people aged 60 years or older; that presented respiratory distress as a symptom; that were obese or immunocompromised; that had cardiac, hepatic, renal, pulmonary or neurologic chronic diseases; and that required ICU admission or invasive respiratory support. COVID-19 represents an enormous challenge for health systems, demanding the need for specialized hospital services. Despite recent advances in vaccination, the absence of effective and scientifically proven treatments makes epidemiological risk analysis studies an even greater need, since early detection and investigation of deaths can act as an indicator for health managers, and in order to optimize the establishment of public policies and early identification of groups of patients that may possibly require specialized assistance.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in relation to the submitted work.

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