v. 3, n. 60, 2023

International Journal of Health Science

FACTORS ASSOCIATED WITH DEATH FROM COVID-19 IN MULTIMORBID PATIENTS

Wesley Araujo Weis
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0000-0002-8506-2774

Pedro Vitor Krüger Dambros
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0000-0002-7979-6800

Diana Goldschmidt Cassimiro da Silva
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0000-0002-2692-1903

Izabela Linetzky
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0000-0002-1016-0185

Eduardo Queiroz Saldanha
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0009-0000-6694-3851

Janeise Martini Peniani Crestani
Universidade do Sul de Santa Catarina - Palhoça
Cuiabá – Mato Grosso
Orcid - 0009-0004-5935-2534

Gabriel Quixabeira Bezerra de Araújo
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0009-0000-3453-6506

Jarbas Ferreira da Silva Segundo
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0009-0006-8740-2396

Pedro Castiglioni Guilherme
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0009-0009-9072-3301

Emerson Giuliano Palacio Favaro
Universidade de Cuiabá
Cuiabá – Mato Grosso
Orcid - 0000-0003-1765-6025

Abstract: Multimorbid patients are a group at high risk of death and the factors associated with death from COVID-19 in these patients are still poorly understood. The aim of the present retrospective cohort study was to identify predictors of death from COVID-19 in multimorbid patients with SARS-CoV-2 infection confirmed by RT-PCR admitted to Brazilian hospitals. Sociodemographic, clinical and hospital characteristics of 3460 patients notified in the National COVID-19 Surveillance were analyzed using a multivariable logistic regression model. Age over 45 years, non-white race/color, respiratory distress, increasing number of chronic diseases, ICU admission and invasive mechanical ventilation increased the risk of death between 1.19 and 9.8 times. On the other hand, asthma, heart disease, diabetes and obesity reduced the risk of death between 0.45 and 0.71 times. Contrary to expectations, chronic lung and kidney diseases were not predictors of death.
More prospective studies must be carried out considering the combinations of chronic diseases and the effects on death from COVID-19.
Keywords: Coronavirus; COVID-19; Intensive Care; Chronic diseases; Multimorbidity.

INTRODUCTION

Infectious diseases have been a challenge to overcome in public health, and currently, there is a pandemic by the new SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) resulting in a differentiated clinical condition called COVID-19. Its treatment (Sanders et al. 2019) and its pathophysiology (Santos et al. 2020) are still not clearly defined, representing an unprecedented health scenario (Gilbert 2020).

COVID-19 has its clinical manifestation characterized by fever, cough, nausea, vomiting, sore throat, ageusia, anosmia,

dyspnea, combinations of these and some patients presenting a nonspecific initial clinical picture that makes diagnosis difficult (Guan et al. 2020, Hung et al. 2020). Additionally, there are cases that can progress to pneumonia, severe acute respiratory syndrome and death (Chen et al. 2020; Xu et al. 2020; Wang et al. 2020).

More severe forms are more likely to develop in people with chronic illnesses (Banerjee et al. 2020; Jordan et al. 2020; Richardson et al. 2020a). Studies have shown a direct association between the burden of morbidities (number and severity) and a higher risk of hospitalization, need for intensive care and death (Meo et al. 2020; Ji et al. 2020; Xie and Chen 2020). A meta-analysis of deaths due to COVID-19 showed that the presence of comorbidities increased the risk of death by 9.4 times when compared to patients without comorbidities (Li et al. 2020). A study in China with more than 70,000 cases identified a high mortality rate in patients with chronic diseases such as heart disease, diabetes and lung disease (Wu and McGoogan 2020). Patients in Italy and China with any of the aforementioned morbidities had a 2.4 times greater risk of mortality (Lippi et al. 2020). A study carried out in the USA and China identified an association between overweight and obesity with a higher risk of admission to intensive care (Zhou et al. 2020). Thus, studies point to the importance of identifying associated factors that can predict and improve the care of multimorbid patients with COVID-19, due to their greater vulnerability to the development of more severe forms and higher risk of death.

In Brazil, multimorbidity is a public health problem and more than half of the population aged over 50 years has multimorbidity for more severe forms of COVID-19, highlighting cardiovascular diseases and obesity as the most frequent conditions regardless of gender (Nunes et al. 2020). Since the beginning of the pandemic, elderly patients represent the highest percentage of deaths from COVID-19, with accumulated lethality rates higher than those found in the general population (Barbosa et al. 2020). A recent study found a 9.8 times greater risk of death in elderly patients with comorbidities compared to those without comorbidities (Galvão and Roncalli 2020). Still, in 2020, Brazil was the Latin American nation with the highest number of confirmed cases and deaths, drawing attention due to the prevalence of chronic morbidities, fragility of the health system, reduced availability of intensive care beds (Lancet 2020), accentuated social inequality (Baqui et al. 2020) and accelerated aging of the population (Lima-Costa et al. 2018). Finally, the high risk of severe COVID-19 in the entire Brazilian population, especially individuals with multimorbidity, reinforces the need for studies involving elderly multimorbid patients (Nunes et al. 2020) and the relationship with COVID-19 (Ji et al. 2020) .

In this scenario, studies on predictive factors for death are important for the rational control of the epidemic and for scientific purposes (Santos et al. 2020) and it becomes an important step for defining strategies for the care of the population with accumulated risk (Nunes et al. . 2019). Thus, the objective of the present study is to identify the factors associated with the death of multimorbid elderly patients admitted to Brazilian hospitals due to COVID-19. Studies with this purpose, including a large sample period (~1 year), based on a cohort, have not yet been published in Brazil.

METHOD

STUDY TYPE AND DATA SOURCE

Retrospective cohort study of multimorbid patients infected with SARS-CoV-2 admitted to the Brazilian hospital network based on COVID-19 Surveillance data provided by the Severe Acute Respiratory Syndrome Surveillance for the year 2020 (Open DATASUS, 2020). The demographic, clinical and hospital data of the patients used are anonymized and in the public domain, meeting the criteria of Resolution n. 466/2012 of the National Health Council for waiver of approval by the Research Ethics Committee (BRASIL, 2012).

STUDY COHORT

Eligible cases for the study cohort were all patients hospitalized for severe acute respiratory syndrome due to COVID-19 positive for SARS-CoV-2 by RT-PCR in detectable samples, with defined outcome of death due to COVID-19 or recovery, with aged between 18 and 95 years, with ≥ 2 chronic diseases (asthma, heart disease, diabetes, liver, obesity, lung disease, kidney) and symptoms/ signs (fever, respiratory distress, dyspnea, cough, O2 saturation < 95%), reported in the period from March 2020 to February 2021. Pregnant or postpartum patients were excluded from the study cohort (Figure 1).

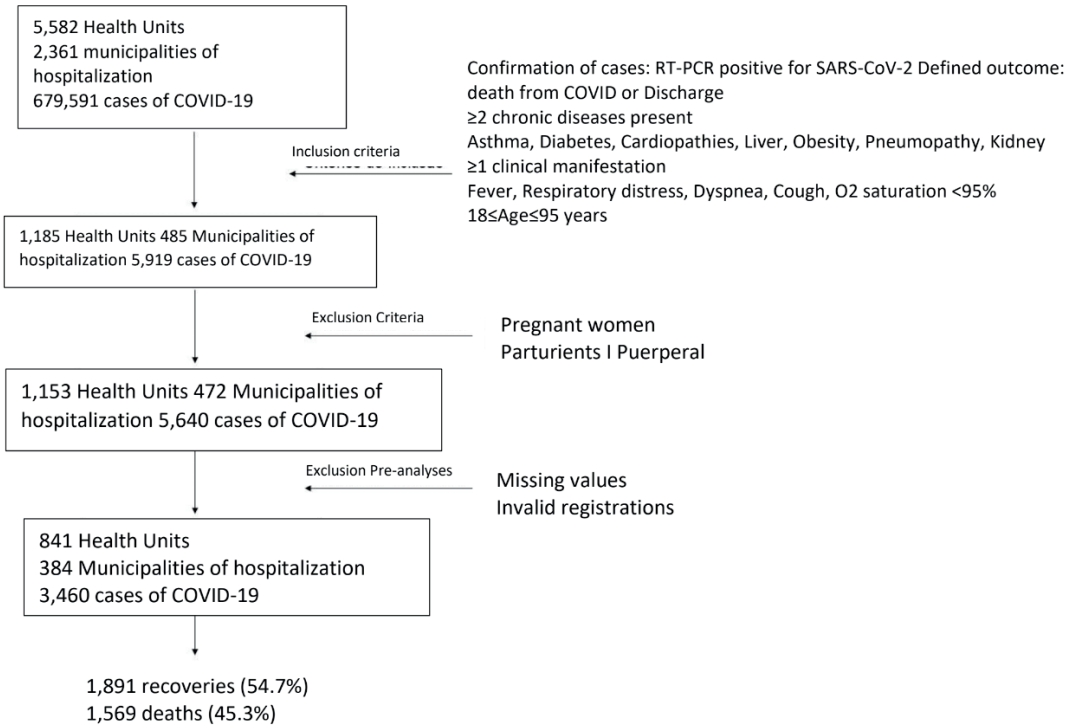


Figure 1. Data extraction flow diagram for the formation of the retrospective cohort of multimorbid patients diagnosed with COVID-19.

STUDY VARIABLES

The variables for the study were age, gender, race/color, chronic diseases, symptoms/signs, nosocomial infection, if admitted to the ICU, use of antivirals and use of ventilatory support. Variables were categorized based on their relative proportions (classes with low frequency were merged) and grouped according to their importance for interpretation.

Age, in complete years, was categorized into age groups 18 to 44, 45 to 70, 71 to 95 years. Race/color was dichotomized into White and Non-White, the latter uniting the black, yellow, brown and indigenous classes. Pre-existing chronic diseases (asthma, heart disease, diabetes, liver, obesity, lung disease, kidney), indicated by yes or no, were added for each patient to represent the number of chronic diseases and categorized into classes 2 and 3 to 5 for descriptions general. Symptoms/signs (fever, respiratory distress, dyspnoea, cough, O2 saturation < 95%) were summed for each patient for general descriptions. Nosocomial infection, ICU admission, use of antivirals, indicated by yes or no, and ventilatory support indicated by no, yes, non-invasive or yes, invasive, were kept as available in the database.

DATA ANALYSIS

The variables were initially evaluated for the internal consistency of their record. Variables with missing records, with contradictory or inconsistent values were excluded from the analyses.

For the description of sociodemographic variables (age, sex, race/color) and clinical (chronic diseases, symptoms/signs) of patients and hospitals (nosocomial, ICU admission, antivirals, ventilatory support), absolute values in the different combinations of the categories of the corresponding variables are presented.

To identify the predictors of deaths from COVID-19, multivariable logistic regression models were built. In these models, all sociodemographic and clinical variables of patients and hospitals were considered independent (candidate predictors) and deaths occurring up to December 2020 as the dependent variable. All candidate predictor variables were included in a first multivariate logistic model and those with statistical significance greater than 0.05 ($p>0.05$) were excluded from subsequent multivariate models. This exclusion process was successively repeated until the final model retained only predictor variables with $p<0.05$, obtaining the effect of each predictor variable controlled by the presence of all other variables and reducing the risks of not detecting confounding. The adjusted odds ratio (OR) parameter obtained by the multivariable logistic model for each predictor variable was interpreted as the risk associated with the occurrence of death. All analyzes were performed using the statistical software R, version 4.1.1 (R Core Team, 2021).

RESULTS

Of the 5640 confirmed cases of COVID-19 admitted to Brazilian hospitals in 2020 included in the study, we analyzed 3460 cases distributed in 841 health units and 384 hospitalization municipalities after excluding potentially confounding patients for non-informative analyzes and records (Figure 1). Of the 3460 confirmed cases of COVID-19 reported in the SRAG-2020, 55.7% (1929 of 3460) of patients were men, and of these 56.7% were white (1095 of 1929) and 53.2% in the age group 45 to 70 years (1027 of 1929). For women, 56% (858 out of 1531) were white and 47.2% (726 out of 1531) aged between 45 and 70 years.

SOCIODEMOGRAPHIC CHARACTERISTICS OF MULTIMORBID PATIENTS WITH COVID-19

The age-sex structure of the cases (Figure 2a,b) points to a high proportion of deaths among men and women, mainly in the age group of 71 to 95 years (54.6%; 857 of 1569), however, with more deaths occurring in men (54.4%; 466 of 857). On the other hand, recoveries occurred mainly between ages 45 and 70 years (57.4%; 1086 of 1891) for both men and women, with men having a higher proportion of recoveries (58.6%; 636 of 1086).

The race-sex structure of the cases (Figure 2c,d) indicates that 55.5% (871 of 1569) of the patients who died were white and of these, 56.6% (493 of 871) were men. A similar pattern is observed for recoveries, 57.2% (1082 of 1891) were white patients and of these, 55.6% (602 of 1082) were men.

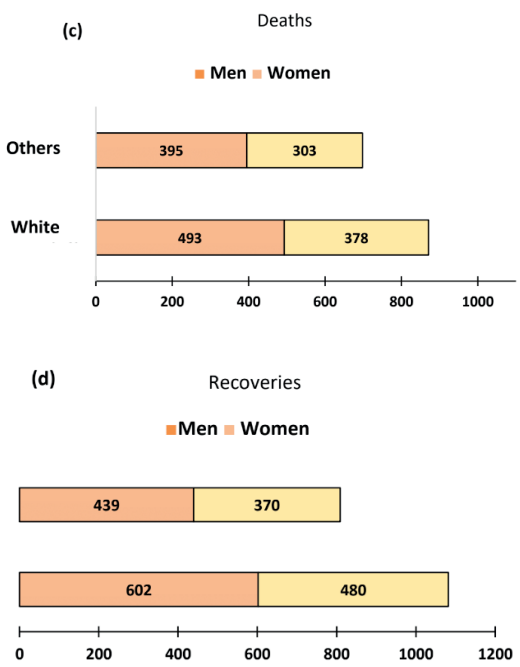
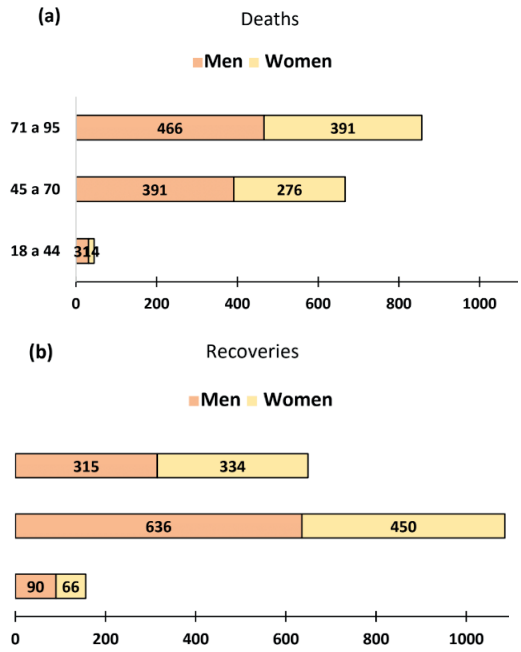


Figure 2. Distribution of cases of deaths and recoveries (discharge/cure) of multimorbid patients diagnosed with COVID-19 according to sex and age group (a,b), sex and race/color (c,d).

CLINICAL CHARACTERISTICS OF MULTIMORBID PATIENTS WITH COVID-19

The main symptoms/signs reported by patients were dyspnea (82.2%; 2843 of 3460), O2 saturation < 95% (77.2%; 2670 of 3460) and respiratory distress (69.8% 2414 of 3460). These three appear in 16 (51.6%) of the 31 symptom/sign combinations and 95.1% (3290 of 3460) of patients had 2 or more symptoms/signs. The predominant combinations of symptoms/signs in deaths (Table 1), deaths in patients with 2 chronic diseases and patients with 3 to 5 chronic diseases were similar, the main combination being fever, respiratory distress, dyspnea, cough and O2 saturation < 95%, with an average representativeness greater than 22%.



The main pre-existing chronic diseases in patients were heart disease (91.0%; 3149 out of 3460) and diabetes (76.2%; 2638 out of 3460), while the least frequent were asthma (6.9%; 240 out of 3460) and liver (1.8%; 63 of 3460). Heart disease and diabetes appear, respectively, in 35 (60.3%) and 22 (37.9%) of the 58 combinations of chronic diseases, and

78% (2700 of 3460) of patients had 2 chronic diseases. The predominant combination in deaths (Table 1), deaths in patients with 2 chronic diseases and patients with 3 to 5 chronic diseases was heart disease and diabetes, with an average representation greater than >45%.

Deaths from COVID-19		**COVID-19 recoveries**	
	N (%)		**N (%)**
Total	1569 (100)		1891(100)
Symptoms/Signs (n=31)		**Symptoms/Signs (n=31)**	
Feb Desc Disp Tos Sat	366 (23,3)	Feb Desc Disp Tos Sat	359 (19,0)
Desc Disp Tos Sat	274 (17,5)	Desc Disp Tos Sat	274 (14,5)
Desc Disp Sat	218 (13,9)	Desc Disp Sat	176 (9,3)
Too much	711 (45,3)	Too much	1082 (57,2)
	N (%)		**N (%)**
	1569 (100)		1891(100)
Chronic diseases (n=50)		**Chronic diseases (n=53)**	
Card Diab	758 (48,3)	Card Diab	1022 (54,0)
Card Diab Rena	110 (7,0)	Card Obes	160 (8,5%)
Card Pneu	100 (6,4)	Card Diab Obes	118 (6,2)
Too much	601 (38,3)	Too much	591 (31,2)
Deaths from COVID-19 Patients with 2 Comorbidities		**Deaths from COVID-19 Patients with 3 to 5 Comorbidities**	
	N (%)		**N (%)**
Total	1176 (100)		1504 (100)
Symptoms/Signs (n=31)		**Symptoms/Signs (n=30)**	
Feb Desc Disp Tos Sat	271 (23,0)	Feb Desc Disp Tos Sat	354 (23,5)
Desc Disp Tos Sat	203 (17,3)	Desc Disp Tos Sat	257 (17,1)
Desc Disp Sat	153 (13,0)	Desc Disp Sat	205 (13,6)
Too much	549 (46,7)	Too much	688 (45,8)
	N (%)		**N (%)**
	1176 (100)		393 (100)
Chronic diseases (n=17)		**Chronic diseases (n=34)**	
Card Diab	758 (64,5)	Card Diab Rena	110 (28,0)
Card Pneu	100 (8,5)	Card Diab Obes	92 (23,4)
Card Rena	87 (7,4)	Card Diab Pneu	51 (13,0)
Too much	231 (19,6)	Too much	140 (47,6)

Table 1. Distribution of concomitant occurrence of symptoms/signs and pre-existing chronic diseases for cases of deaths and recoveries of multimorbid patients diagnosed with COVID-19.

The patients' age-sex structure (Figure 3a,b) revealed that 2 chronic diseases were more frequent both in men (1522 (78.9%) out of 1929) and in women (1178 (76.9%) out of 1531), but in men it was mainly in the age group 45 to 70 years old (803 (78.2%) out of 1027) and in women in the age group 71 to 95 years old (560 (77.2%) out of 725). The race-

sex structure (Figure 3c,d) also revealed that 2 chronic diseases were more frequent in white men (79.3%; 868 of 1095) compared to white women (75.5; 648 of 858).

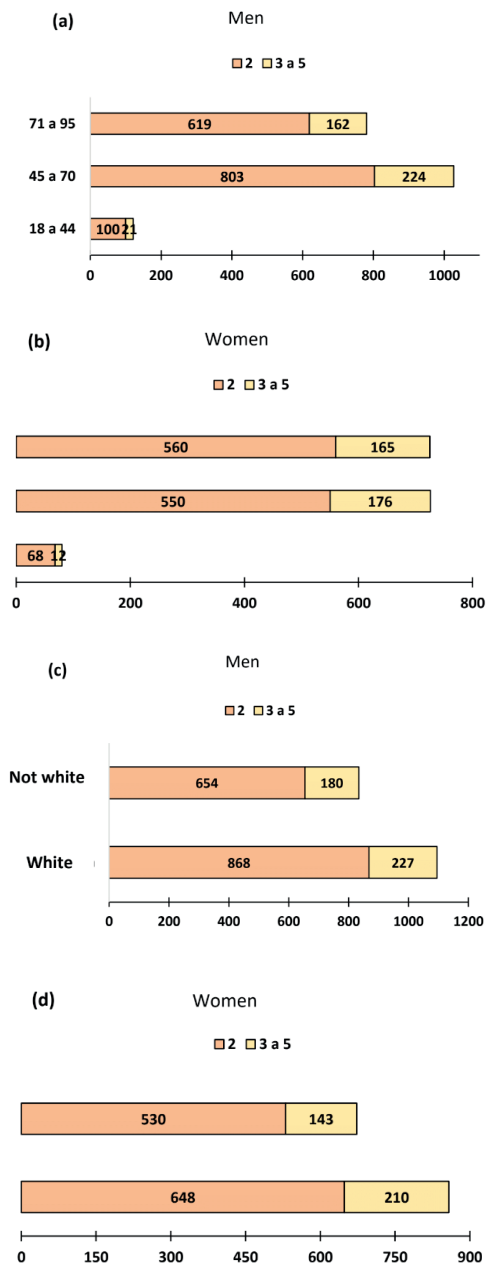


Figure 3. Distribution of chronic diseases present in multimorbid patients diagnosed with COVID-19 according to sex and age group (a,b), sex and race/color (c,d).

HOSPITAL CHARACTERISTICS OF MULTIMORBID PATIENTS WITH COVID-19

Of the 3460 cases hospitalized for COVID-19, 48.4% (1676) were admitted to the ICU and of these, 64.5% (1081) died, mainly in the age group of 71 to 95 years (52.3%; 562 of 1081) (Figure 4a). Of the 1784 (51.6%) patients who were not admitted to the ICU, 27.3% (488) died (Figure 4 b).

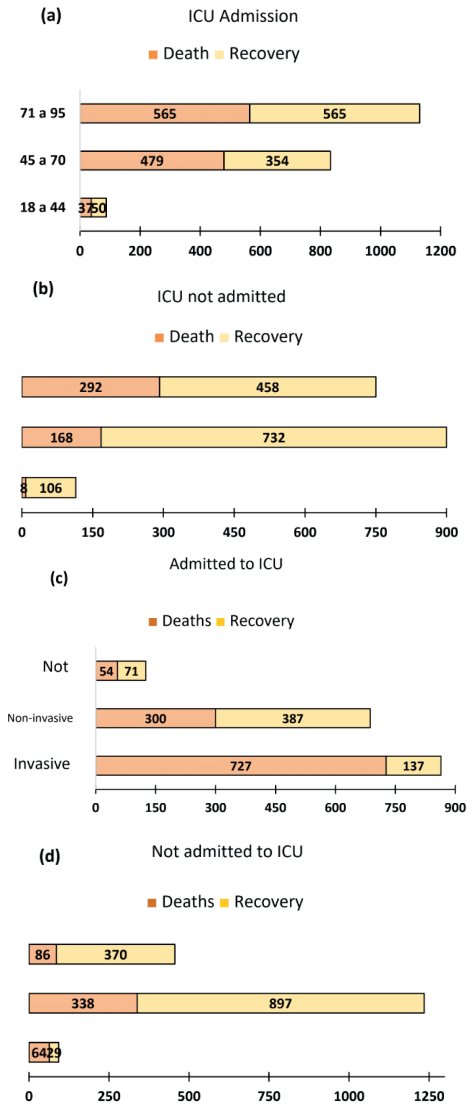


Figure 4. Distribution of cases of deaths and recoveries (discharge/cure) of multimorbid patients diagnosed with COVID-19 according to ICU admission and age group (a,b), ventilatory support (c,d).

Of the 1081 patients admitted to the ICU who died, 67.2% (727) received invasive ventilatory support (Figure 4c). On the other hand, of the 488 patients not admitted to the ICU who died, 69.2% (338) received non-invasive ventilatory support (Figure 4d).

A total of 3.4% (117 of 3460) cases of COVID-19 were reported as infection acquired after hospitalization (nosocomial transmission). Of the 3460 patients hospitalized for COVID-19, only 18% (624) received antiviral treatment and of these, 52.9% (330) were admitted to the ICU and 44.9% (280) died.

PREDICTORS OF DEATHS IN MULTIMORBID PATIENTS WITH COVID-19

The first logistic multivariate model with all covariates showed that sex (OR=1.04; 95%CI=0.88-1.22), fever (OR=1.05; 95%CI=0.89-1.24), dyspnea (OR=1.06; CI95%=0.85-1.33), O2 saturation < 95% (OR=1.12; CI95%=0.913-1.38), cough (OR=0.90 ; 95%CI=0.75-1.07), chronic liver disease (OR=0.79; 95%CI=0.41-1.52), kidney disease (OR=1.30; 95%CI=0.93- 2.16), pneumopathies (OR=0.93; 95%CI=0.67-1.29), nosocomial transmission (OR=1.47; 95%CI=0.932-2.33) and use of antivirals (OR= 0.89; 95%CI=0.72-1.11) were not factors associated with death from COVID-19. The covariables race/color, age, respiratory distress, asthma, heart disease, diabetes, obesity, number of chronic diseases, ventilatory support and ICU admission showed a statistically significant association, controlled for all other covariates. These variables were then entered into a second multivariate logistic model.

In the second multivariate model, all covariates remained statistically significant, being independent factors associated with death from COVID-19 (Figure 5). The risk of death increased by 19% for non-white patients. For the more advanced age groups, the risk of death increased, being 2.1 times higher in the age group between 45 and 70 years old and 5.4 times higher in the age group between 71 and 95 years old. Pre-existing chronic illnesses were associated with death both positively and negatively. The risk of death increased by 54% in patients with respiratory distress and 66% for each chronic disease combined. On the other hand, the risk of death was reduced by 55% in patients with asthma, 44% in patients with heart disease, 29% in patients with diabetes and 45% in patients with obesity. For the hospital variables admission to the ICU and use of ventilatory support, the risk of death increased by 2.28 times in patients admitted to the ICU, 9.8 times in patients who needed invasive ventilatory support and 35% for non-invasive ventilatory support.

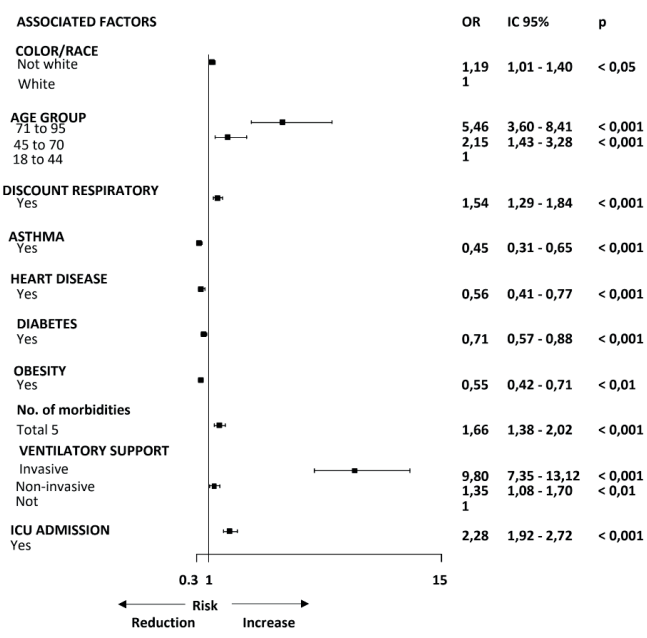


Figure 5. Multivariate analysis to identify factors associated with deaths of multimorbid patients diagnosed with COVID-19.

DISCUSSION

Our study analyzed a cohort of multimorbid patients with SARS-CoV2 confirmed by RT-PCR admitted to the Brazilian hospital

network to identify predictors of death from COVID-19 in these patients. We identified 10 independent predictors of deaths. Age over 45 years, non-white race/color, respiratory distress, increasing number of chronic diseases, ICU admission and invasive mechanical ventilation increased the risk of death between 1.19 and 9.8 times. On the other hand, asthma, heart disease, diabetes and obesity reduced the risk of death between 0.45 and 0.71 times.

Previous studies report that multiple comorbidities occur in older male patients hospitalized with COVID-19 (Emani et al. 2020; Guan et al. 2020b; Liu et al. 2020; Nunes et al. 2020; Yang et al. 2020; Wang et al. 2020; 2020b; Zhou et al. 2020). The risk of death from COVID-19 in these patients is related to changes in the responsiveness of the immune system due to aging (Opal et al. 2005) and the increase in the inflammatory process associated with multimorbidity (Madjid et al. 2020; Friedman et al. Shorey 2019). However, in our study, sex was not a predictive factor for the occurrence of deaths and this can be partially explained by the high proportion of deaths occurring in both men and women aged over 45 years in our study cohort.

As in other studies, non-white patients had an increased risk of death when compared to white patients (Andrade et al. 2020; Santos et al. 2020; Zhang et al. 2020). A possible explanation for this association is that non-white individuals represent the fraction of the Brazilian population with employment conditions that force them not to comply with preventive isolation and protection measures, making them more exposed to infection, with less access to information and services. of health (Santos et al. 2020).

In our study, the increasing number of chronic diseases was a risk factor associated with death from COVID-19, consistent with other published studies (Galvão and Roncalli 2020; Andrade et al. 2020; Macedo et al. 2020; Soares et al. 2020). The combination of different chronic health conditions increases the body's inflammatory state and can cause a metabolic disorder and thus weaken the immune system, putting the multimorbid patient at greater risk of death (Geng et al. 2021). However, multimorbidity showed opposite associations for chronic diseases alone. Chronic liver and kidney diseases and lung diseases were not predictors of death, while asthma, heart disease, diabetes and obesity were protective factors. Other studies show that not all comorbidities have the same strength of association with death as a predictive factor (Emani et al. 2020; Paroham et al. 2020; Zhou et al. 2020). Patients with liver diseases are already reported not to be at greater risk of death from COVID-19 (España et al. 2021). The absence of risk associated with death in lung disease patients may be due to the fact that these patients have some kind of preconditioning effect due to their own pulmonary pathophysiology, thus resulting in better outcomes for these patients. The protective action of asthma and heart disease may be related to the beneficial effects of the anti-inflammatory and anticoagulant properties of the medications used by asthmatic and cardiac patients, exerting a protective function against the course of COVID-19 and, consequently, reducing the risk of death in these patients (Group et al. 2020; Reiner et al. 2020; Rodrigues-Diez et al. 2020; Sivaloganathan et al. 2020). Diabetes, despite being one of the most prevalent diseases in patients with COVID-19, its association with outcomes in these patients is not yet fully understood (Filardi and Morano 2020; Shi et al. 2020; Scheen et al. 2020).

The association of respiratory distress, ICU admission and use of ventilatory support with the increased risk of death can be explained by the fact that they are all clearly related to the

most severe and critical cases of COVID-19, as reported by other studies (Richardson et al. 2020b; Suleyma et al. 2020; Esteban et al. 2009). This explanation is reinforced, in our study, by the high proportion of patients admitted to the ICU who required ventilatory support (92.5%) and of these, also the high proportion of patients who died (64.7%).

Our study has limitations and must be considered. We used secondary data that did not contain information about the status of chronic conditions (control and treatment) or specification of these diseases. Second, both comorbidities and deaths from COVID-19 may be underestimated because only hospitalized patients were included in the study cohort. Third, the use of RT-PCR confirmation of SARS-CoV-2 may result in only the most severe COVID-19 cases being included. However, this study has qualities that deserve to be mentioned. It includes a large sample and geographic coverage involving many health units and hospitalization municipalities.

CONCLUSION

Multimorbid patients have an increased risk of death from COVID-19 aged over 45 years, non-white skin color, admission to the ICU, use of ventilatory support, and an increasing number of chronic diseases. Contrary to expectations, some chronic diseases were not independent factors for the risk of death, such as lung and kidney disease, while others were independent factors protective against death, such as heart disease and diabetes (more prevalent). More prospective studies must be carried out considering the combinations of chronic diseases and the effects on death from COVID-19.

REFERENCES

ANDRADE, L. A.; GOMES, D. S.; LIMA, S. V. M. A.; et al. COVID-19 mortality in an area of northeast Brazil: epidemiological characteristics and prospective spatiotemporal modelling. Epidemiol Infect, 148(e288), e288. 2020. DOI: 10.1017/S0950268820002915

BARBOSA, I. R.; GALVÃO, M. H. R.; SOUZA, T. A.; et al. Incidência e mortalidade por covid-19 na população idosa brasileira e sua relação com indicadores contextuais: um estudo ecológico. Rev Bras Geriatr Gerontol, 23(1), e200171. 2020.

BANERJEE, A.; PASEA, L.; HARRIS, S.; et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. Lancet, 395, 1715-1725. 2020.

BAQUI, P.; BICA, I.; MARRA, V.; et al. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. Lancet Glob Health, 8, e1018-e1026. 2020.

BRASIL. Ministério da Saúde. Conselho Nacional de Saúde. Resolução n. 466, de 12 de dezembro de 2012. Aprova diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Brasília: Diário Oficial da União, 12 dez. 2012.

CHEN, N.; ZHOU, M.; DONG, X.; et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 395, 507-513. 2020.

EMAMI, A.; JAVANMARDI, F.; PIRBONYEH, N.; AKBARI, A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med, 8(1), e35. 2020.

ESPAÑA, P. P.; BILBAO, A.; GARCÍA-GUTIÉRREZ, S.; et al. Predictors of mortality of COVID-19 in the general population and nursing homes. Intern Emerg Med, 16(6), 1487-1496. 2021. DOI: 10.1007/s11739-020-02594-8.
ESTEBAN, C.; QUINTANA, J. M.; MORAZA, J.; et al. Impact of hospitalisations for exacerbations of COPD on health-related quality of life. Respir Med, 103(8), 1201-1208. 2009.

FILARDI, T.; MORANO, S. COVID-19: is there a link between the course of infection and pharmacological agents in diabetes?. J Endocrinol Invest, 43(8), 1053-1060. 2020. DOI: 10.1007/s40618-020-01318-1.

FRIEDMAN, E.; SHOREY, C. Inflammation in multimorbidity and disability: an integrative review. Health Psychol, 38, 791-801. 2019.

GALVÃO, M. H. R.; RONCALLI, A. G. Fatores associados a maior risco de ocorrência de óbito por COVID-19: análise de sobrevivência com base em casos confirmados. Rev Bras Epidemiol, 23, e200106. 2020.

GENG, M. J.; WANG, L. P.; REN, X.; et al. Risk factors for developing severe COVID-19 in China: an analysis of disease surveillance data. Infect Dis Poverty, 10, 48. 2021. DOI: 10.1186/s40249-021-00820-9.

GILBERT, G. L. Commentary: SARS, MERS and COVID-19 - new threats, old lessons. International Journal of Epidemiology, 49, 726-728. 2020.

GUAN, W.; NI, Z.; HU, Y.; et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med, 382, 1708-1720. 2020.

GUAN, W. J.; LIANG, W. H.; ZHAO, Y.; et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A Nationwide analysis. Eur Respir J, 55(5), 2000547. 2020.

GROUP RC, HORBY, P.; LIM, W. S.; EMBERSON, J. R.; MAFHAM, M.; BELL, J. L.; et al. Dexamethasone in Hospitalized Patients with Covid-19—Preliminary Report. N Engl J Med, Epub. 2020.

HUANG, C.; WANG, Y.; LI, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 395, 497-506. 2020.

JI, D.; ZHANG, D.; XU, J.; et al. Prediction for progression risk in patients with COVID-19 pneumonia: the CALL Score. Clin Infect Dis, 71, 1393-1399. 2020.

JORDAN, R. E.; ADAB, P.; CHENG, K. K. Covid-19: risk factors for severe disease and death. BMJ, 368, m1198. 2020.

MACEDO, M. C.; et al. Correlation between hospitalized patients' demographics, symptoms, comorbidities, and COVID-19 pandemic in Bahia, Brazil. PLoS One, 15, e0243966. 2020.

COVID-19 in Brazil: "so what?". The Lancet, 395, 1461. 2020.

LI, L. Q.; HUANG, T.; WANG, Y. Q.; et al. Covid-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol, 92(6), 577-583. 2020.

LIMA-COSTA, M. F.; ANDRADE, F. B.; SOUZA, P. R. B.; et al. The Brazilian Longitudinal Study of Aging (ELSI-Brazil): objectives and design. Am J Epidemiol, 187, 1345-1353. 2018.

LIPPI, G.; MATTIUZZI, C.; SANCHIS-GOMAR, F.; et al. Clinical and demographic characteristics of patients dying from COVID-19 in Italy versus China. J Med Virol, 92, 1759-1760. 2020.

LIU, H.; CHEN, S.; LIU, M.; NIE, H.; LU, H. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. Aging Dis, 11(3), 668-678. 2020.

MADJID, M.; PAYAM, S. N.; SOLOMON, S. D.; VARDENY, O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol, 5, 831-840. 2020.

MEO, S. A.; ALHOWIKAN, A. M.; AL-KHLAIWI, T.; et al. Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur Rev Med Pharmacol Sci, 24(4), 2012-2019. 2020.

NUNES, B. P.; SOUZA, A. S. S. de; NOGUEIRA, J.; et al. Multimorbidade e população em risco para COVID-19 grave no Estudo Longitudinal da Saúde dos Idosos Brasileiros. Cad Saúde Pública, 36(12), e00129620. 2020.

NUNES, B. P.; BATISTA, S. R. R.; ANDRADE, F. B.; SOUZA JUNIOR, P. R. B.; et al. Multimorbidity: the Brazilian Longitudinal Study of Aging (ELSI-Brazil). Rev Saúde Pública, 52(Suppl 2), 10s. 2019.

OPAL, S. M.; GIRARD, T. D.; ELY, E. W. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis, 41(Suppl 7), S504-S512. 2005.

OPEN DATASUS. Brasil (2020) Ministério da Saúde. Secretaria de Vigilância em Saúde. Open Date SARS COV 19. Ministério da Saúde. [Online]. Disponível em: https://opendatasus.saude.gov.br/dataset/bd-srag-2020 (Acessado em 07 mar. 2021).

PAROHAN, M.; YAGHOUBI, S.; SERAJI, A.; JAVANBAKHT, M. H.; SARRAF, P.; DJALALI, M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. Aging Male, 2020, p. 1-9.

R CORE TEAM. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Disponível em: https://www.R-project.org/ (Acessado em [data de acesso]).
REINER, Ž.; HATAMIPOUR, M.; BANACH, M.; et al. Statins and the COVID-19 main protease: in silico evidence on direct interaction. Arch Med Sci, 16(3), 490-496. 2020.

RICHARDSON, S. J.; CARROLL, C. B.; CLOSE, J.; et al. Research with older people in a world with COVID-19: identification of current and future priorities, challenges and opportunities. Age Ageing, 49(6), 901-906. 2020.

RICHARDSON, S.; HIRSCH, J. S.; NARASIMHAN, M.; et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA, 323(20), 2052-2059. 2020. DOI: 10.1001/jama.2020.6775.

RODRIGUES-DIEZ, R. R.; TEJERA-MUÑOZ, A.; MARQUEZ-EXPÓSITO, L.; et al. Statins: could an old friend help in the fight against COVID-19? Br J Pharmacol, 177(21), 4873-4886. 2020.

SANDERS, J. M.; MONOGUE, M. L.; JODLOWSKI, T. Z.; et al. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA, 323, 1824-1836. 2020.

SANTOS, M. M.; LUCENA, E. E. S.; LIMA, K. C.; et al. Survival and predictors of deaths of patients hospitalised due to COVID-19 from a retrospective and multicentre cohort study in Brazil. Epidemiology and Infection, 148, e198, 1-11. 2020.

SCHEEN, A. J.; MARRE, M.; THIVOLET, C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. Diabetes Metab, 46(4), 265-271. 2020.

SHI, Q.; ZHANG, X.; JIANG, F. et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center retrospective study. Diabetes Care, 3(7), 1382-1391. 2020.

SIVALOGANATHAN, H.; LADIKOU, E. E.; CHEVASSUT, T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol, 190(4), e192-e195. 2020.

SOARES, R. d. C. M.; MATTOS, L. R.; RAPOSO, L. M. Risk factors for hospitalization and mortality due to COVID-19 in Espírito Santo State, Brazil. The American Journal of Tropical Medicine and Hygiene, 103, 1184-1190. 2020.

SULEYMAN, G.; FADEL, R. A.; MALETTE, K. M.; HAMMOND, C.; ABDULLA, H.; ENTZ, A.; et al. Clinical Characteristics and Morbidity Associated With Coronavirus Disease 2019 in a Series of Patients in Metropolitan Detroit. JAMA Network Open, 3(6), e2012270. 2020.

WANG, X.; FANG, X.; CAI, Z.; et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: a systemic review and meta-analysis. Research (Wash DC), 2020b, 2402961.

WANG, D.; HU, B.; HU, C.; et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA, 2020, 323, 1061-9.

WU, Z.; MCGOOGAN, J. M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA, 2020, 323, 1239-42.

XIE, M.; CHEN, Q. Insight into 2019 novel coronavirus – an updated interim review and lessons from SARS-CoV and MERS-CoV. International Journal of Infectious Diseases, 2020, 94, 119-124.

XU, X. W. et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ, 2020, 368, m606.

YANG, J. et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis, 2020, 94, 91-95.

ZHANG, J. et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clinical Microbiology and Infection, 26, 767-772, 2020.

ZHOU, F. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: retrospective cohort study. Lancet, 395, 1054-1062, 2020.