Survival of patients with diabetes mellitus hospitalized for acute respiratory syndrome due to COVID-19

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ABSTRACT

Given the magnitude of COVID-19 and the increase in hospitalization cases for severe acute respiratory syndrome (SARS), especially among patients with diabetes mellitus, it is essential to understand the epidemiological aspects inherent to the disease and the worsening of cases. Thus, this study aimed to analyze the survival of patients with diabetes mellitus hospitalized for SARS due to COVID-19 in different regions of Brazil. This is a longitudinal study, carried out based on data reported in the Influenza Epidemiological Surveillance Information System during the year 2020. The number of patients with diabetes mellitus among the hospitalized cases of SARS due to COVID-19 in the different regions of Brazil and the lethality rate among them were identified. A comparison of patient profiles of those who survived or did not survive and the Cox regression analysis were performed to evaluate the factors associated with shorter survival of patients. It was found that 51.4% of patients hospitalized with SARS due to COVID-19 had diabetes, and the case lethality rate among them was 45.0%. The Northeastern and Northern regions presented a higher proportion of patients with diabetes mellitus (56.5% and 54.3%, respectively) and a higher lethality rate (53.8% and 59.9%, respectively). The mean survival time of cases with diabetes mellitus hospitalized for SARS due to COVID-19 was estimated to be 35.7 days (0.5 days). A lower survival rate was observed among residents of the Northeastern and Northern regions with skin color reported as non-white, who required admission to Intensive Care Units and invasive mechanical ventilation, and presented respiratory symptoms such as dyspnea, respiratory distress and an oxygen saturation lower than 95%. It is concluded that diabetes mellitus was responsible for the high occurrence and lethality, mainly in the Northeastern and Northern regions, among non-white patients and those with greater clinical severity, which reinforces the importance of taking measures aimed at supporting this population.

KEYWORDS: Diabetes mellitus. COVID-19. Severe acute respiratory syndrome. Survival analysis. Pandemics.

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INTRODUCTION

The novel coronavirus, identified in China in 2019 as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been responsible for the morbidity and mortality of thousands of people due to the disease named COVID-19[1]. This disease can be manifested in an asymptomatic form or with mild symptoms, mimicking a case of Influenza-Like Illness (ILI) – especially when affects young

people and children – as well as in a severe form, causing pneumonia, severe acute respiratory syndrome (SARS) and organ failure, particularly in the elderly (> 60 years old) and people with heart, lung, or endocrine comorbidities, such as diabetes mellitus[2,3].

Studies have shown that the presence of comorbidities such as diabetes mellitus is strongly associated with increased complications and hospitalizations for SARS due to COVID-19[4,5]. In China, a study performed in a hospital considered a benchmark for COVID-19 treatment showed that patients with diabetes and affected by the novel coronavirus disease had an increased risk of severe pneumonia, excessive inflammatory responses, and hypercoagulability when compared to those who were not diagnosed with diabetes[6]. A meta-analysis including 33 studies concluded that diabetes mellitus is associated with a worse prognosis in patients with COVID-19, having a twofold increase in the risk of dying compared to patients who do not present this comorbidity[7].

In Brazil, a study conducted up until the 21st epidemiological week of 2020 showed that diabetes mellitus was more frequent in individuals hospitalized with SARS due to COVID-19 when compared to the country's general population[8]. Other studies conducted with patients hospitalized for SARS showed an association between mortality and diabetes mellitus, corroborating the results of many international studies[5,7,9,10].

In March 2020, when the community transmission of COVID-19 was declared, the Health Surveillance Department of the Brazilian Ministry of Health (SVS/MS) carried out the adaptation of the Acute Respiratory Syndrome Surveillance System, aiming to guide the National Health Surveillance System for the simultaneous flow of SARS-CoV-2, influenza and other respiratory viruses, in order to assist the efforts of healthcare professionals[11].

In this scenario, regarding the health surveillance measures, the mandatory notification and monitoring of hospitalized cases and deaths by SARS in the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) – developed to provide updated information in order to support the decision-making by managers and healthcare providers for the prevention and management of this disease – are highlighted[12,13]. However, for the SIVEP-Gripe to fulfill its purpose and for the health surveillance measures to be effective, it is necessary to have qualified personnel assigned to it, to provide this information promptly and for this measure not to be regarded as a mere bureaucratic task but as the initial step for planning measures aiming to reduce the impacts of COVID-19, especially among the most vulnerable people[14].

Given the magnitude of COVID-19 and the increase in SARS hospitalizations, especially among patients with diabetes mellitus, it is necessary to produce comprehensive studies to specifically evaluate the behavior of this disease in the different regions of Brazil.

Therefore, this study aims to analyze the survival of patients with diabetes mellitus hospitalized for SARS due to COVID-19 in different regions of Brazil.

MATERIALS AND METHODS

This is an observational, longitudinal study related to the epidemiological surveillance of cases of patients with diabetes mellitus hospitalized for SARS nationwide due to COVID-19 in 2020. The study population consisted of all cases of patients with diabetes mellitus hospitalized for SARS registered in SIVEP-Gripe between the 1st and the 63th epidemiological weeks of 2020.

COVID-19 infection was assumed when patients tested positive on the RT-PCR or the SARS-CoV-2 infection tests. People with SARS who required admission to the Intensive Care Unit (ICU) or needed invasive or non-invasive ventilatory support were classified as SARS-critical. The source of information used was the secondary, anonymous, unidentified database of individuals from the SIVEP-Gripe for the year 2020, which was updated on April 26th, 2021[15].

The variables of interest were as follows: epidemiological week of the onset of first symptoms; evolution (death and recovery); evolution date; Brazilian region of residence and hospitalization; sex (male, female); age (years); skin color (non-white, white); signs and symptoms; ICU admission; ventilatory support (invasive and non-invasive).

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical software (version 23.0, IBM, Armonk, NY, USA). Descriptive and inferential analyses were performed. The Kolmogorov–Smirnov's test was used to assess the variables' normality. For the descriptive analysis, absolute and relative frequency distributions, central tendency measures, and variability measures were used, according to the result of the normality test.

The number of patients with diabetes mellitus among the cases of SARS hospitalized for COVID-19 in the different regions of Brazil and the case lethality rate among them were identified. A comparison of the characteristics of patients who survived and those who did not was carried out in order to identify the differences between them. Categorical variables were compared using the Pearson's Chi-squared test. For the numerical variables, the Mann–Whitney's test was used, due to the absence of normality in the data distribution. Values of $p < 0.05$ were considered as statistically significant differences.

To evaluate the factors associated with the survival of critical COVID-19 patients, a survival analysis was performed, considering the observation time as the dependent variable, indicating the end of observation time (censoring). The Kaplan–Meier's estimator was used to estimate the probability of survival of critical COVID-19 patients.

To identify the statistical significance between survival curves the Log-rank test was applied, adopting as a significant difference the variables that presented p < 0.05. The variables with statistical significance were included in the multivariate analysis using the Cox regression. The Hazard Ratio (HR) and their respective 95% Confidence Intervals (95% CI) were estimated. Since this was a study that only included secondary data from the public domain, of free and open access, without identifying the research participants, the approval by the Research Ethics Committee for Research with Human Beings was not required. Consent was not obtained due to the data being anonymous and in the public domain.

RESULTS

During the 1st and the 63th epidemiological weeks of 2020, a total of 563,051 SARS-hospitalized cases were reported, of which 429,010 were due to COVID-19. Of these, 222,111 (51.8%) provided information regarding the presence or absence of diabetes mellitus. A total of 114,144 (51.4%) cases of diabetes mellitus were identified.

Regarding the geographical distribution of cases, it was found that the Northeastern and Northern regions showed a higher proportion of patients with diabetes mellitus among the SARS-hospitalized cases due to COVID-19, with 56.5% and 54.3%, respectively, according to Table 1.

The case lethality rate of SARS due to COVID-19 among patients with diabetes mellitus was 45.0%, corresponding to 51,378 deaths in Brazil nationwide in 2020.

Regarding the profile of patients with diabetes mellitus hospitalized for SARS who survived or those who did not, a prevalence of deaths was observed among patients living in the Northern (59.9%) and Northeastern (53.8%) regions, with higher median age (70 vs. 63 years), male (54.3%), who required admission to the Intensive Care Unit (67.4%), required IMV (51.0%), and presented symptoms of dyspnea (86.1%), respiratory distress (77.5%) and SpO$_2$ < 95% (82.9%), as shown in Table 2.

The mean survival time of patients with diabetes mellitus hospitalized for SARS due to COVID-19 was estimated to be 35.7 days (mean standard error of 0.5 days). Table 3 shows the univariate analysis results of the variables associated with patient survival based on the Kaplan–Meier estimate.

In the multivariate analysis, using Cox regression, it was found that cases residing in the Northern and Northeastern regions had a lower survival rate when compared to those residing in the Central-western region. Conversely, cases residing in the Southern region had a higher survival rate than patients from the Central-western region.

Regarding socio-demographic and clinical profiles, an association was found between shorter survival and patients whose skin color was declared as non-white, patients who required ICU admission, who required IMV, and who presented respiratory symptoms such as dyspnea, respiratory distress and SpO$_2$ < 95%. The presence of fever, coughing, odynophagia, diarrhea and aging were associated with longer patient survival, as shown in Table 4.

DISCUSSION

Diabetes mellitus was considered a comorbidity of high occurrence among patients hospitalized for SARS nationwide, with a higher proportion of cases being patients living in the Northeastern and Northern regions. Lower survival was also found among residents of the Northeastern and Northern regions, who self-declared as non-white, who required ICU admission, required IMV, and who presented symptoms such as dyspnea, respiratory distress and/or SpO$_2$ < 95%.

Diabetes mellitus is a comorbidity of public health importance. In the Brazilian population, it is estimated that

Table 1 - Geographic distribution of patients with diabetes mellitus hospitalized for SARS due to COVID-19 in 2020, Brazil.

Region	Patients with diabetes mellitus (n = 114,144)	p-value*
Northern Region	4,957 (54.3%)	Ref.
Northeastern Region	18,607 (56.5%)	<0.001
Central-western Region	9,698 (46.2%)	<0.001
Southeastern Region	62,003 (52.7%)	<0.003
Southern Region	18,879 (45.6%)	<0.001

*Pearson's Chi-squared test, statistically significant (p < 0.05); Ref.= Reference used.

Table 2 - The profile of patients with diabetes mellitus hospitalized for SARS due to COVID-19 who survived or those who did not in 2020, Brazil (n = 114,144).

Variables	Survived (n = 81,704)	Did not survive (n = -65,977)	p-value*
Region of residence (n = 114,144)			<0.001[a]
Northern Region	1,990 (40.1)	2,967 (59.9)	Ref.
Northeastern Region	8,593 (46.2)	10,014 (53.8)	<0.001[a]
Central-western Region	5,584 (57.6)	4,114 (42.4)	<0.001[a]
Southeastern Region	35,568 (57.4)	26,435 (42.6)	<0.001[a]
Southern Region	11,031 (58.4)	7,848 (41.6)	<0.001[a]
Age in years (n = 114,144) median (Q$_1$-Q$_3$)	63.0 (54.0–72.0)	70 (62.0-79.0)	<0.001[b]
Sex (n = 114,130)			<0.001[a]
Female	30,423 (48.5)	23,496 (45.7)	
Male	32,334 (51.5)	27,877 (54.3)	
Skin color (n = 90,355)			<0.001[a]
Non-white	21,323 (43.9)	20,340 (48.7)	
White	27,241 (56.1)	21,451 (51.3)	
ICU admission (n = 106,129)			<0.001[a]
No	41,141 (70.2)	15,506 (32.6)	
Yes	17,456 (29.8)	32,026 (67.4)	
Required IMV (n = 102,986)			<0.001[a]
No	52,431 (91.9)	22,506 (49.0)	
Yes	4,620 (8.1)	23,429 (51.0)	
Signs and symptoms			
Fever (n = 100,221)	37,877 (67.9)	29,539 (66.5)	<0.001[a]
Coughing (n = 103,091)	46,240 (80.3)	34,609 (76.1)	<0.001[a]
Odynophagia (n = 85,409)	10,265 (21.5)	7,167 (19.1)	<0.001[a]
Dyspnea (n = 104,268)	44,019 (77.2)	40,704 (86.1)	<0.001[a]
Respiratory distress (n = 96,947)	33,794 (64.1)	34,301 (77.5)	<0.001[a]
SpO$_2$ < 95% (n = 100,162)	38,489 (70.5)	37,752 (82.9)	<0.001[a]
Diarrhea (n = 85,415)	9,615 (20.0)	6,040 (16.1)	<0.001[a]
Vomit (n = 83,772)	5,501 (11.7)	3,852 (10.5)	<0.001[a]
Abdominal pain (n = 50,434)	23,149 (7.4)	1,451 (6.8)	<0.001[a]
Fatigue (n = 52,461)	9,373 (31.0)	6,491 (29.2)	<0.001[a]
Anosmia (n = 50,656)	4,544 (15.5)	2,113 (9.9)	<0.001[a]
Ageusia (n = 50,551)	4,609 (15.7)	2,098 (9.9)	<0.001[a]

Values refer to the total of valid answers; missing data were not considered; Ref. = Reference used (the region with the highest proportion of deaths among patients with diabetes mellitus); ICU = intensive care unit; IMV = invasive mechanical ventilation; SpO$_2$ = oxygen saturation; *Statistically significant (p < 0.05); [a]Pearson's Chi-squared test; [b]Mann–Whitney's test.

the prevalence of diabetes mellitus is 9.2%, with a higher occurrence in the Southeastern region (12.8%), followed by the Northeastern region (12.2%). The prevalence in the Central-western (7.6%), Southern (7.2%) and Northern (6.3%) regions is lower, which demonstrates regional disparities[16].

Data from the Epidemiological Bulletin of the Ministry of Health indicated that 65.7% of SARS deaths due to COVID-19, notified between the 8th and the 53rd epidemiological weeks of 2020, had at least one comorbidity or risk factor for the disease, with heart disease and diabetes mellitus being the most frequent conditions[17]. Studies suggest that patients with diabetes are at a higher risk of developing severe forms of COVID-19 such as pneumonia and SARS, leading to a worse prognosis and, consequently, a lower survival rate[18,19].

Table 3 - Results of Log-rank test analysis for factors associated with the survival of patients with diabetes mellitus hospitalized for SARS due to COVID-19 in 2020, Brazil (n = 114,144).

Variable	Estimate survival (days) mean (error)	Log-rank (p-value) *
Region of residence		<0.001
Northern Region	25.8 (0.6)	
Northeastern Region	29.4 (0.6)	
Central-western Region	33.7 (0.9)	
Southeastern Region	40.2 (0.9)	
Southern Region	34.8 (0.8)	
Age (Age group)		0.866
0 to 19 years old	42.3 (7.3)	
20 to 59 years old	29.0 (3.5)	
≥ 60 years old	19.8 (2.1)	
Sex		0.020
Female	36.5 (0.7)	
Male	34.8 (0.7)	
Skin color		<0.001
Non-white	32.8 (0.7)	
White	34.9 (0.8)	
ICU admission		<0.001
No	48.8 (1.5)	
Yes	30.2 (0.5)	
Required IMV		<0.001
No	50.4 (1.3)	
Yes	22.0 (0.3)	
Signs and symptoms		
Fever		<0.001
No	35.3 (0.8)	
Yes	36.5 (0.7)	
Coughing		<0.001
No	34.2 (0.9)	
Yes	36.8 (0.7)	
Odynophagia		0.013
No	36.1 (0.7)	
Yes	37.3 (1.1)	

Variable	Estimate survival (days) mean (error)	Log-rank (p-value) *
Signs and symptoms		
Dyspnea		<0.001
No	48.5 (2.0)	
Yes	32.9 (0.5)	
Respiratory distress		<0.001
No	45.9 (1.6)	
Yes	31.5 (0.5)	
$SpO_2 < 95\%$		<0.001
No	43.4 (1.5)	
Yes	32.8 (0.5)	
Diarrhea		<0.001
No	36.0 (0.7)	
Yes	38.2 (1.5)	
Vomit		0.001
No	36.0 (0.7)	
Yes	37.5 (1.4)	
Abdominal pain		0.804
No	37.7 (0.9)	
Yes	34.2 (1.5)	
Fatigue		0.912
No	38.2 (1.0)	
Yes	33.7 (0.9)	
Anosmia		<0.001
No	37.2 (0.9)	
Yes	38.3 (1.9)	
Ageusia		<0.001
No	37.0 (0.9)	
Yes	40.1 (2.1)	

ICU = intensive care unit; IMV = invasive mechanical ventilation; SpO_2 = oxygen saturation; *Statistically significant ($p < 0.05$).

Results found regarding the survival of patients with diabetes and with SARS due to COVID-19 in different regions may be associated with the socioeconomic disparities and access to health services that exist among Brazilian regions, as the availability and access to resources for disease management and control of complications directly impact survival rates[8].

The Northern and Northeastern regions presented the highest proportion of diabetes patients hospitalized for SARS due to COVID-19 in 2020, as well as the highest in-hospital lethality. In contrast, the lowest proportion of cases and lowest lethality were found in the Southern region. The heterogeneity presented by Brazil in relation to the evolution of the pandemic and social determinants may justify the differences found among its regions, given that the differences in population distribution patterns, transportation conditions, income, and education inequalities are determining factors for the transmission, severity, and lethality of COVID-19[20].

Furthermore, a study based on data available at the

Table 4 - Results of the final multivariate Cox regression model for factors associated with death in patients with diabetes mellitus hospitalized for SARS due to COVID-19 in 2020, Brazil (n = 114,144).

Variable	HR	95% CI	p-value*
Central-western Region	-	-	<0.001
Northern Region	1.136	1.065–1.212	<0.001
Northeastern Region	1.084	1.024–1.147	0.006
Southern Region	0.813	0.768–0.854	<0.001
Southeastern Region	0.993	0.945–1.043	0.766
Non-white skin color	1.044	1.013–1.077	0.006
ICU admission	1.045	1.009–1.083	0.014
Required IMV	1.814	1.755–1.875	<0.001
Fever	0.929	0.904–0.956	<0.001
Coughing	0.906	0.879–0.934	<0.001
Odynophagia	0.954	0.918–0.991	0.016
Dyspnea	1.184	1.140–1.230	<0.001
Respiratory distress	1.168	1.130–1.207	<0.001
$SpO_2 < 95\%$	1.152	1.1123–1.194	<0.001
Diarrhea	0.942	0.906–0.981	0.003
Ageusia	0.889	0.847–0.933	<0.001

*Statistically significant (p < 0.05).

Information Technology Department of the Unified Health System (Datasus) showed inequality in the distribution of ICU beds for patients with COVID-19 among the Brazilian regions. In relation to public beds, the Southeastern region concentrates 43.2% of the ICU beds, while the Northern region has 6.9%; in the case of private hospital beds, the Southeastern region concentrates 51.7% of the ICU beds, while the Northern region has 5.8%, contradicting the principle of equity[21]. There is heterogeneity in the distribution of beds per inhabitant among the different regions of Brazil. In the Southeastern and Southern regions, the proportion of public ICU beds is 1.8 beds/10,000 inhabitants. In the Central-western region, the proportion is 1.2 beds/10,000 inhabitants. In the Northeastern and Northern regions, the proportion is even smaller, with 1.0 and 0.9 beds/10,000 inhabitants, respectively[22].

In this study, lower survival rates were found among patients who self-declared as non-white, corroborating data found in the United States, where the infection and mortality rates found were higher in the black population compared to the white population; in addition, higher risks of hospitalization, ICU admission, and death were identified in black, brown, and yellow people[23].

A study conducted in Brazil also demonstrated that having black or brown skin color is the second most important risk factor for the outcome of mortality, second only to the factor 'age', thus reinforcing the relevance of social determinants[24]. There is an important relationship between social determinants, multimorbidity and COVID-19, where individuals with the worst socioeconomic conditions are the most affected[24]. Lower-income and educational level, along with poor living conditions and difficult access to health services, can contribute to the transmission of COVID-19 and the development of its complications in the population self-declared as non-white[25]. In this context, the importance of social determinants of health are emphasized, especially in pandemics[25].

Moreover, studies conducted in the United States and China corroborate the findings of this study by identifying that patients with diabetes mellitus hospitalized due to COVID-19 have a greater need for ICU admission, intubation and IMV use, in addition to higher risks for complications involving respiratory failure, multiple organ damage, and sepsis. These variables can be considered severity indicators of the clinical case presented by patients, and it is known that the greater the severity presented by these patients, the more it will negatively impact their survival time[6,16,26-28].

It is worth mentioning that the time of diagnosis of diabetes mellitus, as well as the adherence to its treatment, can also influence the health status of patients, as poorly managed diabetes mellitus is a risk factor for several infectious diseases[29]. Type II diabetes mellitus, which affects elderly patients the most, has a silent onset. Most

patients only receive the diagnosis when they have a complication resulting from high blood glucose levels, which contributes to the greater severity of the clinical condition[30].

In Scotland, the risks of complications due to COVID-19 or a greater need for ICU admission were extremely high in the population with diabetes, unlike the population without this comorbidity, which reinforces the greater susceptibility to complications of this population[31]. A meta-analysis conducted in China showed that patients with diabetes presented higher serum levels of inflammatory biomarkers, such as C-reactive protein, IL-6, serum ferritin, and coagulation index, making them more susceptible to an inflammatory storm and consequent worsening of COVID-19. Thus, justifying the greater need for ICU admissions as well as IMV use by these patients, which may contribute to lower survival rates[6].

A meta-analysis that studied specific symptoms and comorbidities that predict severe COVID-19 and ICU admission demonstrated that the novel coronavirus can generate asymptomatic cases, especially in young patients without comorbidities, as SARS with high rates of morbidity and mortality in patients who are in older age groups and/or with comorbidities. According to the study, dyspnea stands out as the most relevant symptom in predicting worse outcomes, and when present, the probability of ICU admission increases 6.6 times compared to those cases where it is absent[32].

In addition, the presence of signs of severity identified in this study, such as dyspnea, respiratory distress, and $SpO_2 < 95\%$ define SARS, which when not managed and controlled quickly and accurately can lead to unfavorable outcomes and decreased chances of survival.

Among the limitations of the study, the inherent limitations of using secondary data are highlighted, such as the possibility of filling errors and missing information in the SIVEP-Gripe records, the under-reporting of cases and deaths by SARS, and also the under-reporting of comorbidities. Furthermore, it was not possible to manage duplicate cases in these records, as no case identification variables exist.

Studying the survival of patients affected by SARS due to COVID-19 is vital for the development of preventive and countermeasures against the pandemic in Brazil, especially among patients with diabetes mellitus, as this is a significantly affected population.

CONCLUSION

It was concluded that diabetes mellitus presented high occurrence and lethality, especially in the Northeastern and Northern regions, in patients who were non-white and with greater clinical severity. It was verified that 51.4% of the hospitalized cases had diabetes mellitus and the lethality rate among them was 45.0%. The results presented show the need to meet the demands of the Brazilian diabetic population, especially in these regions, considering the specificities of each one. Moreover, understanding how the social determinants of health contribute to the incidence, prevalence, treatment, and mortality associated with COVID-19 may favor the development of more effective interventions to address the pandemic.

AUTHORS' CONTRIBUTIONS

SMS contributed to the design and development of the study, data collection and analysis, interpretation of results, writing and final review of the manuscript; APCQ contributed to the design and development of the study, data collection, interpretation of results, writing and final review of the manuscript; MCBS contributed to the design and development of the study, data collection, interpretation of results and final review of the manuscript; IRM contributed to the design and development of the study, data collection, interpretation of results, writing and final review of the manuscript; BACF contributed to the design and development of the study, data collection and analysis, interpretation of results and final review of the manuscript; AGS contributed to the design and development of the study, data collection, interpretation of results and final review of the manuscript; LVT contributed to the design and development of the study, data collection and analysis, interpretation of results, writing and final review of the manuscript. All authors approved the final version for publication.

FUNDING

REFERENCES

1. Brasil. Secretaria de Vigilância em Saúde. Guia de vigilância epidemiológica: emergência de saúde pública de importância nacional pela doença pelo coronavírus 2019 - COVID-19. ed. prelim. Brasília: Ministério da Saúde; 2021. [cited 2022 Oct 3]. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/guias-e-manuais/2021/guia-de-vigilancia-epidemiologica-covid-19-3.pdf/view

2. Shin CH, Kim KH, Jeeva S, Kang SM. Towards goals to refine prophylactic and therapeutic strategies against COVID-19 linked to aging and metabolic syndrome. Cells. 2021; 10:1412.

3. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. J Microbiol Immunol Infect. 2020;53:404-12.

4. Killerby ME, Link-Gelles R, Haight SC, Schrodt CA, England L, Gomes DJ, et al. Characteristics associated with hospitalization among patients with COVID-19: Metropolitan Atlanta, Georgia, March-April 2020. MMWR Morb Mortal Wkly Rep. 2020;69:790-4.

5. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu, L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109:531-8.

6. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;36:e3319.

7. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19?: a meta-analysis. Diabetes Metab Syndr. 2020;14:535-45.

8. Niquini RP, Lana RM, Pacheco AG, Cruz OG, Coelho FC, Carvalho LM, et al. Description and comparison of demographic characteristics and comorbidities in SARI from Covid-19, SARI from influenza, and the Brazilian general population. Cad Saude Publica. 2020;36:e00149420.

9. Prado PR, Gimenes FR, Lima MV, Prado VB, Soares CP, Amaral TL. Risk factors for death due to COVID-19, in the state of Acre, Brazil, 2020: a retrospective cohort study. Epidemiol Serv Saude. 2021;30:e2020676.

10. Ranzani OT, Bastos LS, Gelli JG, Marchesi JF, Baião F, Hamacher S, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. Lancet Respir Med. 2021;9:407-18.

11. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Guia de vigilância epidemiológica: emergência de saúde pública de importância nacional pela doença pelo coronavírus 2019 - COVID-19. Brasília: Ministério da Saúde; 2022. [cited 2022 Oct 3]. Available from: https://portaldeboaspraticas.iff. fiocruz.br/biblioteca/guia-de-vigilancia-epidemiologica-covid-19-ms-2022/

12. Brasil. Ministério da Saúde. Roteiro para capacitação de usuários no uso do SIVEP-Gripe. [cited 2022 Oct 3]. Available from: https://dvs.portovelho.ro.gov.br/uploads/editor/files/ EPIDEMIOLOGIA/Apresenta%C3%A7%C3%A3o%20 SIVEP-Gripe.pdf

13. Ribeiro IG, Sanchez MN. Evaluation of the severe acute respiratory syndrome (SARS) surveillance system, with emphasis on influenza, Brazil, 2014-2016. Epidemiol Serv Saude. 2020;29:e2020066.

14. Lana RM, Coelho FC, Gomes MF, Cruz OG, Bastos LS, Villela DA, et al. The novel coronavirus (SARS-CoV-2) emergency and the role of timely and effective national health surveillance. Cad Saude Publica. 2020;36:e00019620.

15. Brasil. Ministério da Saúde. SRAG 2020: banco de dados de síndrome respiratória aguda grave: incluindo dados da COVID-19. [cited 2022 Oct 3]. Available from: https:// opendatasus.saude.gov.br/dataset/srag-2020

16. Muzzy J, Campos MR, Emmerick I, Silva RS, Schramm JM. Prevalência de diabetes mellitus e suas complicações e caracterização das lacunas na atenção à saúde a partir da triangulação de pesquisas. Cad Saude Publica 2021; 37:e00076120.

17. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico Especial: doença pelo coronavírus COVID-19: semana epidemiológica 53 (27/12/2020 a 2/1/2021). [cited 2022 Oct 3]. Available from: https://www. gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/ epidemiologicos/covid-19/2021/boletim_epidemiologico_ covid_44.pdf

18. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe COVID-19 with diabetes. BMJ Open Diabetes Res Care. 2020;8:e001343.

19. Lima BS, Frota MC, Ramos SP, Pereira Júnior JL, Nóbrega Neto AD. Diabetes mellitus e sua relação com a COVID-19: um panorama atual proveniente de uma revisão sistemática. Res Soc Develop. 2021;10:e384101522598.

20. Viacava F, Bellido JG. Health, access to services and sources of payment, according to household surveys. Cien Saude Colet. 2016;21:351-70.

21. Cotrim Junior DF, Cabral LM, Asensi FD. Oferta de leitos de UTI no Brasil à luz dos princípios constitucionais da igualdade e da universalidade em tempos de COVID-19. Rev Direito Publico. 2020;17:198-225.

22. Associação de Medicina Intensiva Brasileira. AMIB apresenta dados atualizados sobre leitos de UTI no Brasil. [cited 2022 Oct 3]. Available from: http://www.epsjv.fiocruz.br/sites/ default/files/files/dados_uti_amib%281%29.pdf

23. Yancy CW. COVID-19 and African Americans. JAMA. 2020;323:1891-2.

24. Baqui P, Bica I, Marra V, Ercole A, van der Schaar M. Ethnicand regional variations in hospital mortalityfrom COVID-19 in Brazil: a crosssectional observational study. Lancet Glob Health. 2020;8:e1018-26.

25. Mascarello KC, Vieira AC, Souza AS, Marcarini WD, Barauna VG, Maciel EL. COVID-19 hospitalization and death and relationship with social determinants of health and morbidities in Espírito Santo State, Brazil: a cross-sectional study. Epidemiol Serv Saude. 2021;30:e2020919.

26. Shrestha E, Charkviani M, Musurakis C, Kansakar AR, Devkota A, Banjade R, et al. Type 2 diabetes is associated with increased risk of critical respiratory illness in patients COVID-19 in a community hospital. Obes Med. 2021;22:100316.

27. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31:1068-77.

28. Tamura RE, Said SM, Freitas LM, Rubio IG. Outcome and death risk of diabetes patients with Covid-19 receiving pre-hospital and in-hospital metformin therapies. Diabetol Metab Syndr. 2021;13:76.

29. Marinho FP, Loyola IS, Monteiro IO, Castro FM, Carvalho MG, Garcia JA, et al. Inter-relação entre COVID-19 e diabetes mellitus: uma revisão sistemática. Res Soc Develop. 2021;10:e4810212191.

30. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: IDF; 2021. [cited 2022 Oct 3]. Available from: https://www.diabetesatlas.org

31. McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LA, McAllister DA, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. Lancet Diabetes Endocrinol. 2021;9:82-93.

32. Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health. 2020;65:533-46.