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Original Article

Influence of simultaneous comorbidities on COVID-associated acute respiratory distress syndrome mortality in people with diabetes

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الملخص

أهداف البحث: هدفت هذه الدراسة إلى تحليل تأثير 23 حالة مرضية مصاحبة على وفيات متلازمة الضائقة التنفسية الحادة المرتبطة بكوفيد، حصريا لدى الأشخاص الذين لديهم تاريخ من مرض السكري.

طريقة البحث: تم استخدام دراسة رصدية وتحليلية ومقطعية للتحقيق في البيانات من 6723 خدمة صحية في البرازيل، تضم 5433 شخصا يعانون من مرض السكري. تم استخدام نماذج الانحدار اللوجستي المعدلة للعوامل الديموغرافية مثل العمر والجنس والعرق لتحليل العلاقة بين وفيات متلازمة الضائقة التنفسية الحادة المرتبطة بكوفيد والأمراض المصاحبة.

النتائج: الأشخاص الذين لديهم اثنين، وثلاثة، وأربعة، وخمسة من الأمراض المصاحبة المتزامنة لديهم فرصة أكبر للوفاة. لقد حددنا أن مرضى السكري الذين يعانون من أمراض استقلابية مصاحبة، أو اضطرابات عصبية، أو كانوا مدخنين لديهم خطر وفاة أعلى متوقع بناء على متلازمة الضائقة التنفسية الحادة المرتبطة بكوفيد.

الاستنتاجات: يلعب عدد الأمراض المصاحبة دورا حاسما في وفيات متلازمة الضائقة التنفسية الحادة المرتبطة بكوفيد لدى مرضى السكري، وخاصة أولئك الذين يعانون من التدخين والأمراض العصبية في وقت واحد.

الكلمات المفتاحية: مرض مرافق؛ مراضة متعددة؛ الوفيات؛ مرض السكري؛ فيروس كورونا المسبب للمتلازمة التنفسية الحادة الوخيمة 2

Abstract

Objectives: This study analyzed the influence of 23 comorbidities on COVID-associated acute distress respiratory syndrome (CARDS) mortality in people with a history of diabetes mellitus.

Methods: An observational, analytical, cross sectional study was utilized to investigate data from 6723 health services in Brazil, comprising 5433 people with diabetes. Adjusted logistic regression models for demographic factors such as age, sex, and race were used to analyze the association between CARDS mortality and comorbidities.

Results: Persons with two ($p < 0.001$), three ($p < 0.001$), four ($p < 0.001$), and five ($p < 0.001$) simultaneous comorbidities had a higher chance of dying. We identified that diabetes patients who had concomitant metabolic diseases ($p = 0.019$), neurological disorders ($p < 0.001$), or were smokers ($p < 0.001$) had a higher predicted mortality risk based on CADRS.

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Conclusion: The number of comorbidities plays a determining role in CARDS mortality in people with diabetes, especially those who suffer from smoking and neurological diseases simultaneously.

Keywords: Comorbidity; Diabetes; Mortality; Multimorbidity; SARS-CoV-2

Introduction

It has been shown that one-third of people with COVID-19 under intensive care have comorbidities (chronic diseases) or multimorbidities, leading to increased length of stay (inpatient care) and cardiovascular failure.[1] However, another study found that >50% of critically ill patients with COVID-19 in intensive care units suffer from comorbidities. In the latter study, it was also observed that the short- and long-term survival rates were high in general medical patients with comorbidities compared to patients without previous chronic conditions, a divergent aspect from the first study cited above.[2]

In the panorama of chronic conditions or comorbidities, patients with a history of diabetes mellitus (HDM) and COVID-associated acute distress respiratory syndrome (CARDS) experience a deleterious bidirectional relationship because, given the hyperglycemia, they are more vulnerable to mechanical ventilation, prolonged hospitalization, and clinical conditions such as ketoacidosis and hyperosmolar hyperglycemia. These aspects add to the healthcare challenges.[3–5]

There is robust molecular evidence that people with HDD have genetic characteristics that favor the development of CARDS. It is also known that euglycemic individuals can develop diabetes after this respiratory syndrome.[6] Epidemiological evidence points to higher mortality from CARDS among people with HDD, especially in the geriatric age group.[7,8]

The cellular and molecular features of CARDS are still not fully understood. However, growing evidence shows a dysregulated immune response with excessive inflammation and hypercoagulation. In addition to these cellular and molecular features, CARDS is also characterized by several systemic abnormalities, including hypoxia and multiorgan dysfunction.[9] People with pre-existing diabetes and other chronic diseases have an increased risk of infections, autoimmune diseases, and cancer.[10]

Some publications worldwide (Hungary, India, Iran, and Nigeria) have demonstrated a relationship between the number of comorbidities and COVID-19 mortality in general patients.[7,11–13] On the other hand, there has been a lack of studies investigating the influence of simultaneous comorbidities on CARDS mortality in people with HDD.[14,15]

The concurrent presence of comorbidities such as diabetes, hypertension, and obesity, in particular, can even triple the mortality from COVID-19 in general or hospital patients.[16] Specifically, regarding individuals with HDD, some research reports have indicated that irrespective of renal and cardiovascular function and body mass index (BMI), having HDD is a risk factor for CARDS mortality.[14,15]

Given the bidirectional relationship mentioned above, some authors have recommended that researchers leave their offices and work closer to patients at the bedside. In other words, it is necessary to study the relationship among CARDS, metabolism, and glucose homeostasis within health services to help manage patients and prevent COVID-19- and diabetes-related deaths.[17]

The studies above, even those with robust samples, were mainly conducted in general patients and analyzed only 10, 7, 6, and 5 comorbidities separately.[12,14–16] In the current investigation, we analyzed the influence of 23 comorbidities on CARDS mortality in people with HDD.

Hypothesis

We hypothesize that in people with an HDD, the mortality rates from CARDS increase in proportion to the number of concurrent comorbidities.

Materials and Methods

Population source

We conducted an observational, analytical cross-sectional study. The data from patients with diabetes mellitus were collected at a single point in time to examine the prevalence of CARDS and its association with comorbidities and CARDS mortality. This activity allowed for the construction of a vast clinical database over 6723 health services in Brazil. The services are distributed in 19 health regions of Maranhão, consisting of 2049 primary health care units, 1246 specialized clinics, 588 support units (small hospitals and centers for diagnosis and treatment), and 404 health units. The state of Maranhão is located in the northeast of Brazil, with approximately 7,075,181 inhabitants and 217 municipalities.

Epidemiological surveillance health professionals have monitored flu syndrome and severe acute respiratory syndrome (SARS) until the outcome of death with the support of a form with 41 questions. These professionals carried out clinical visits, in some cases according to the health service routine. Healthcare professionals only conducted epidemiological surveillance visits for patients who required hospitalization, in order to monitor their progression to death and/or discharge. Between March 2020 and January 2022, 386,567 cases were registered on the Notification System, of which 10,986 progressed to death.

This notification is a mandatory activity in health services in the state of Maranhão, Brazil. Patients were interviewed to answer the instrument's 41 questions, and these data were sent to the national system called SIVEP-Gripe Brazilian Ministry of Health. This notification system developed passive epidemiological surveillance of SARS in Brazilian health services since the influenza A (H1N1) pandemic. From this, SARS surveillance was implemented in the surveillance network for influenza and other respiratory viruses, which previously operated exclusively with sentinel surveillance of

flu syndrome. In 2020, COVID-19 surveillance was incorporated into the surveillance network for influenza and other respiratory viruses.

Participants

Participants consisted of patients with HDD of both sexes, regardless of age, diagnosed with CARDS and at least one comorbidity in addition to diabetes. Based on these eligibility criteria, the final sample consisted of 5433 patients.

Criteria for defining death related to CARDS

The definition of death due to CARDS covered clinical, epidemiological, or laboratory criteria. The epidemiological criteria consisted of the death of a patient with close or home contact in the previous 7 days with a laboratory-confirmed case of COVID-19. Besides that, the death of a patient who resided or worked in an area with a high risk of virus transmission (e.g., nursing homes for the elderly or homeless people) with up to 7 days of clinical symptoms and the death of a health professional (hospital environment) with up to 7 days of clinical symptoms was also considered as an epidemiological criterion for death.

The laboratory criterion consisted of the death of a person with clinical symptoms in the last 7 days and a molecular biology (detectable result for SARS-CoV-2 by quantitative PCR) or antigen research (reagent result for SARS-CoV-2 by immunochromatography) test.

Data collection

Some characterization variables were analyzed for the sample study (sex, age group, race, health service where the patient was treated, diagnostic criteria, and type of exam) besides 23 preexisting comorbidities, as follows:

(1) Arterial hypertension
(2) Obesity
(3) Cardiovascular disease
(4) Neurological disease
(5) Metabolic disease
(6) Respiratory disease
(7) Cancer
(8) Kidney disease
(9) Smoking
(10) Gastric disease
(11) Alcoholism
(12) Liver disease
(13) HIV-AIDS
(14) Psychiatric disorder
(15) Autoimmune diseases
(16) Rheumatological disease
(17) Leprosy
(18) Malformation
(19) Urological disease
(20) Chemical dependency
(21) Hematologic disease
(22) Dermatological disease
(23) Rare disease

Data analysis

We conducted univariate and bivariate analyses using the free JAMOVI (version 1.6.23; RMM software, Sidney, Australia) to describe the distribution of variables across our study population and identify preliminary associations between various comorbidities and CARDS mortality. The purpose was to provide a foundational understanding of the data, which informed the direction of our more complex analyses. On the other hand, we also prepared contingency tables to study the frequency of deaths according to the distribution of type and number of comorbidities simultaneous to diabetes, using the chi-square test.

The specific mortality rate for selected causes was calculated as follows.[18]

$$\frac{\textit{Number of deaths of people with diabetes and specific comorbidities between January 2020 and March 2022}}{\textit{Number of deaths of people with diabetes and any comorbidity between January and March 2022}} \times 100$$

Once this initial step was completed, we will move on to the correlation between variables using the Spearman correlation coefficient.

We constructed a binary logistic regression model adjusted for age group and sex. The core of our analysis involved logistic regression, performed to assess the relationship between each comorbidity and the risk of CARDS mortality, adjusted for sex, age, and race. This model was chosen for its ability to elucidate the independent effects of each comorbidity on mortality, accounting for potential confounders. In the logistic regression models, we included comorbidities both individually and in combination to assess their independent and cumulative effects on mortality. This approach allowed us to isolate the effect of each comorbidity on CARDS mortality while controlling for demographic factors, thereby providing a more nuanced understanding of how these conditions interact and contribute to death in individuals with diabetes.

The adjustments for demographic factors in our regression models were carefully chosen based on existing literature indicating their potential confounding effects on the relationship between comorbidities and mortality outcomes.[19,20] By adjusting for these factors, we presented a more accurate and nuanced analysis that reflects the real-world complexity of CARDS mortality risk in individuals with diabetes. We analyzed the odds ratio in a 95% confidence interval (95% CI) to determine the degree of risk.

Results

Patient characteristics

The overall sample investigated in our study was predominantly older adults (about 56%) from Brazil (57%), with a balanced distribution of males and females. The predominant diagnostic criterion for COVID-19 infection was the rapid test. Regarding health care, we observed a predominance of attendance to public services.

Distribution by race showed significant variation in deaths, particularly among Brown people, followed by White, Asian, Black, and Indigenous people, suggesting racial disparities in the outcomes of CARDS. The diagnostic criteria demonstrated an overwhelming predominance of laboratory tests confirming cases among those who died ($p < 0.001$), with the majority of deaths diagnosed in public laboratories and through RT-PCR (Table 1).

Table 1: Characteristics of patients with HDD, ARDS, and simultaneous comorbidity. Maranhão, Brazil. 2023.

Variable		N	%
Age range	0–19 years	13	0.2
	20–29 years	47	0.9
	30–39 years	220	4
	40–49 years	580	10.7
	50–59 years	984	18.1
	60–70 years	1557	28.7
	>70 years	2024	37.3
Sex	Female	2511	46.2
	Male	2922	53.8
Skin color	Yellow	494	9.1
	White	901	16.6
	Indigenous	22	0.4
	Brown	3096	57
	Black	459	8.4
Death	Yes	3235	59.5
	No	2198	40.5
Diagnostic criteria	Clinical examination	6	0.1
	Clinical exam and tomography	28	0.5
	Laboratory tests	5.398	99.4
Type of laboratory	Public	4.838	89
	Private	549	10.1
Type of exam	Serological	83	1.5
	Quick Test	3179	58.5
	RT-PCR	2.139	40

Mortality rate among HDD people

The mortality rate for people with diabetes was approximately 60% (Table 1). Deaths occurred predominantly among older adults aged >70 (31.4%), adults between 60 and 70 years ($p < 0.001$), and males (55.9%) ($p < 0.001$). Regarding race, the mortality rates were highest among Brown people (63.5%) ($p < 0.001$). We did not observe statistically significant differences between the number of comorbidities and participants' race ($p = 0.691$).

Simultaneous comorbidities in people with HDD and CARDS

Most of the participants in this study (46.8%) and those who died (27.9%) had three simultaneous comorbidities such as diabetes and at least two more chronic health conditions ($p < 0.001$) (Table 2). Individuals with two (95% CI: 0.21–0.34; $p < 0.001$), three (95% CI: 0.51–0.65; $p < 0.001$), four (95% CI: 0.25–0.37; $p < 0.001$), and five (95% CI: 0.10–0.25; $p < 0.001$) comorbidities had significantly higher odds of dying from CARDS. The percentage of males with up to four comorbidities (51.4%) was higher than that of females (45.2%) ($p < 0.001$). Men with diabetes and comorbidities (95% CI: 0.73–0.90; $p < 0.001$) were more likely to die than women with the same disease. After adjusting the model for the number of comorbidities, the statistical difference remained between the sexes (95% CI: 0.71–0.89; $p < 0.001$).

In this investigation, the mean number of comorbidities was significantly higher in deceased patients (2.67 ± 1.12) compared to those discharged (2.27 ± 1.10), with both groups presenting a median of 3.00 comorbidities ($p < 0.001$; Mann–Whitney). The Kolmogorov–Smirnov test confirmed that the data were not normally distributed ($p < 0.001$). Our findings highlight a significant association between the number of comorbidities and patient mortality. Despite the identical medians, the significance of the Mann–Whitney U test suggests a disparity in the distribution of comorbidities, potentially indicating that the range or severity of comorbidities, beyond their mere count, may influence patient outcomes (Figure 1).

When we studied the association of this outcome with the simultaneous presence of comorbidities, we found that the most robust ones were linked to hypertension ($p < 0.001$), cardiovascular disease ($p < 0.001$), kidney disease ($p < 0.001$), and obesity ($p < 0.001$). Many other robust associations were verified but with few expressive samples concerning the total sample (Table 3).

Table 2: Comparison between the frequency of concurrent comorbidities and the outcome of death from ARDS in people with HDD. Maranhão, Brazil. 2023.

		Number of concurrent diabetes comorbidities								
Death		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Total**	**p-value[a]**
Yes	N (%)	736 (13.5)	361 (6.6)	1517 (28)	482 (8.8)	128 (2.3)	8 (0.1)	3 (0.0)	3235 (59.5)	<0.001
No	N (%)	859 (15.8)	115 (2.1)	1027 (19)	172 (3)	24 (0.4)		1 (0.0)	2198 (40.4)	
Total	N (%)	1595 (29.3)	476 (8.7)	2544 (46.8)	654 (12)	152 (2.8)	8 (0.1)	4 (0.0)	5433	

[a] Chi-square test.

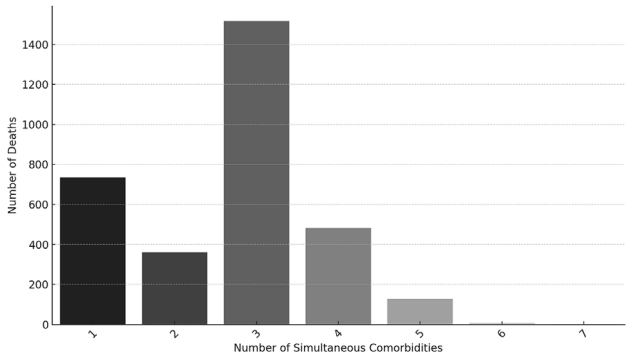

Figure 1: Distribution of deaths according to the number of simultaneous comorbidities in people with diabetes. Maranhão, Brazil. 2023.

When we built a logistic regression model, a different scenario was obtained. In the initial model, the most impacting comorbidities for death from CARDS in people with diabetes were hypertension (95% CI: 1.28−1.60; $p < 0.001$), respiratory disease (95% CI: 1.23−2.69; $p = 0.003$), cardiovascular disease (95% CI: 1.66−2.50; $p < 0.001$), kidney disease (95% CI: 2.09−4.08; $p < 0.001$), cancer (95% CI: 1.72−7.93; $p < 0.001$), obesity (95% CI: 2.48−5.65; $p < 0.001$), neurological disease (95% CI: 2.80−7.87; $p < 0.001$), smoking (95% CI: 3.67−17.38; $p < 0.001$), and metabolic disease (95% CI: 11.65).

After adjusting for variables including age, sex, and race, the comorbidities with the highest prediction for mortality were metabolic disease (95% CI: 1.48−84.31; $p = 0.019$), smoking (95% CI: 3.39−16.38; $p < 0.001$), and neurological disease (95% CI: 1.54−87.89; $p = 0.017$) (Table 4). Some comorbidities were not found in the sample such as rare, urological, and dermatological diseases.

Table 3: Distribution of mortality from ARSS among patients with HDD and concurrent comorbidities. Maranhão, Brazil. 2023.

Concurrent diabetes comorbidities	Mortality Rate		
	N	%	p-value[a]
Hypertension	2.132	69.9	<0.001
Cardiovascular disease	411	12.7	**<0.001**
Kidney disease	200	6.1	**<0.001**
Obesity	155	4.7	**<0.001**
Neurological disease	121	3.7	**<0.001**
Respiratory disease	102	3.1	**<0.001**
Smoking	89	2.7	**<0.001**
Cancer	46	1.4	**<0.001**
Psychiatric disorder	27	0.8	0.122
Metabolic disease	23	0.7	**<0.001**
Liver disease	19	0.5	**0.024**
Alcoholism	13	0.4	**0.011**
Gastric disease	14	0.4	0.356
Leprosy	8	0.2	0.073
HIV-AIDS	7	0.2	**0.029**
Rheumatologic disease	7	0.2	0.932
Autoimmune disease	4	0.1	0.351
Chemical dependency	3	0.0	**0.015**
Hematological disease	3	0.0	0.529
Malformation	2	0.0	**0.002**

Values of $p < 0.05$ at the 95% significance level are represented in bold.
[a] Chi-square test.

Table 4: Impact of concurrent diabetes comorbidities on the outcome of death from ARDS. Maranhão, Brazil. 2023.

Model	Predictor	Odds ratio	Confidence interval		p-value
			Lower	Upper	
1	Hypertension	1.43	1.28	1.60	**<0.001**
	Cardiovascular disease	2.04	1.66	2.50	**<0.001**
	Kidney disease	2.92	2.09	4.08	**<0.001**
	Obesity	3.74	2.48	5.65	**<0.001**
	Neurological disease	4.70	2.80	7.87	**<0.001**
	Respiratory disease	1.82	1.23	2.69	**0.003**
	Smoking	7.99	3.67	17.38	**<0.001**
	Cancer	3.70	1.72	7.93	**<0.001**
	Metabolic disease	11.65	1.54	87.89	**0.017**
2	Hypertension	1.44	1.28	1.62	**<0.001**
	Cardiovascular disease	2.01	1.64	2.46	**<0.001**
	Kidney disease	2.87	2.05	4.01	**<0.001**
	Obesity	3.86	2.55	5.83	**<0.001**
	Neurological disease	4.67	2.78	7.82	**<0.001**
	Respiratory disease	1.86	1.26	2.76	**0.002**
	Smoking	7.68	3.53	16.72	**<0.001**
	Cancer	3.69	1.71	7.93	**<0.001**
	Metabolic disease	12.08	1.59	91.29	**0.016**
3	Hypertension	1.45	1.29	1.63	**<0.001**
	Cardiovascular disease	2.01	1.63	2.48	**<0.001**
	Kidney disease	3.05	2.16	4.30	**<0.001**
	Obesity	3.97	2.60	6.05	**<0.001**
	Neurological disease	4.54	2.69	7.67	**<0.001**
	Respiratory disease	1.97	1.31	2.95	**0.001**
	Smoking	7.46	3.39	16.38	**<0.001**
	Cancer	3.82	1.75	8.31	**<0.001**
	Metabolic disease	11.19	1.48	84.31	**0.019**

Model 1: With no adjustment.
Model 2: Adjusted for age group, and gender.
Model 3: Adjusted for age group, gender, and skin color.
Values of $p < 0.05$ at the 95% significance level are represented in bold.

Discussion

Based on the data final analysis model proposed, we identified a model fitting measure classification value of 87% (in relation to logistic regression in Tale 4) in this study, which supports the arguments presented throughout the discussion of our findings. This is interesting, considering that not only regarding CARDS but also across various public health issues, there is growing discussion about the ability of cross-sectional studies to offer insights into preliminary causal relationships.[21,22]

Complexity of comorbidities and treatment implications

In our sample of persons with HDD, the comorbidities with the most significant potential to increase the chances of

death were metabolic, smoking, and neurological diseases. These findings differ from those of prior studies, which concluded that the simultaneous presence of diabetes/hypertension and obesity, diabetes and kidney disease, diabetes and cardiovascular disease, and diabetes and high BMI predict death from COVID-19 in persons with HDD.[12,14–16]

These differences confirm the lack of unanimity on the relationship between the presence of comorbidities and higher mortality from CARDS in subjects with HDD; thus, this topic still needs to be further explored in longitudinal epidemiological or case–control studies. This observation calls for a comprehensive and personalized approach to patient care. CARDS treatment in individuals with HDD must take into account their associated comorbidities since these conditions often exacerbate one another. Furthermore, multimorbidity can worsen due to the poor management of a single metabolic comorbidity with systemic action.

Metabolic disease

Our study highlights the central role of metabolic diseases in CARDS mortality in individuals with HDD. Metabolic diseases encompass various conditions affecting amino acid, carbohydrate, and lipid metabolism. The high odds ratio associated with metabolic diseases underscores the need for the meticulous management of these conditions. On the other hand, this high odds ratio study may have been influenced by the high sample size resulting from many chronic health conditions included in the same notification. While metabolic diseases encompass various health issues, the potential systemic effects of metabolic dysfunction should not be underestimated. Targeted interventions addressing diabetes and metabolic comorbidities can be crucial in reducing ARDS-related mortality in this population.

With the above consideration in mind, amino acid metabolism acts as an essential signaling pathway and is a potential and strategic target for immunity and control of COVID-19 infection. For example, the metabolism of arginine collaborates with the replication of the coronavirus by helping the binding of spike protein to the angiotensin-converting enzyme 2 (ACE-2) receptor and acting as a substrate for the massive production of nitric oxide in lung tissues, causing hyperinflammation and tissue damage. On the other hand, amino acids such as glycine, glutamine, serine, and tryptophan may be beneficial in the acute phase of COVID-19 due to biological actions such as cytotoxicity, macrophage recruitment, and the reduction of inflammation.[23,24]

The relationship between metabolic diseases and other chronic conditions (obesity, hypertension, and cardiovascular disease) in CARDS cases indicates the need for health professionals to strengthen their knowledge about nutrition and food.[25] One of the lessons learned from the COVID-19 pandemic is that nutrition and managing chronic conditions are imperative for an adequate immune response to COVID-19.[26] Precisely because it interacts with various morbidities and even lifestyle (as in the case of nutrition and diet), caution is needed in attributing too much weight to metabolic disease in cases of CARDS deaths in people with diabetes.

Smoking: A multifaceted risk factor

Smoking is another significant predictor of ARDS mortality among people with HDD. The association between smoking and CARDS is multifaceted, involving increased susceptibility to viral infections, increased ACE-2 receptor expression, and the potential to worsen glycemic homeostasis.[27–29] Given the substantial influence of smoking on CARDS outcomes, smoking cessation interventions should be an integral part of patient treatment, highlighting the need to understand the broad implications of smoking on health and its role in comorbidity-related mortality in individuals with HDD.

Neurological diseases: A vulnerable population

Our findings indicate that individuals with HDD and neurological diseases face a disproportionately high risk of CARDS-related mortality. This observation is in accordance with previous research suggesting that neurological comorbidities can contribute to severe clinical infections.[14,30]

Many authors have also shown the manifestation of post-COVID-19 neurological alterations in their studies. We believe that the high odds ratio identified in this study is justified by the incidence of cases of diabetes with poor glycemic and metabolic management (another aggravating factor in this bidirectional relationship).[31–33] These complex interactions among neurological conditions, diabetes, and CARDS warrant further investigations to develop tailored treatment approaches for this vulnerable group.

Limitations and implications

While our study provides essential insights into the relationship between comorbidities and CARDS mortality in individuals with HDD, we must acknowledge its limitations. The data were not specifically collected for this study, potentially introducing biases. For example, we needed access to information such as hospitalization period, the evolution of biochemical data, medication intake, and vaccination. Another noteworthy limitation was our inability to categorize the severity of CARDS cases (mild, moderate, or severe). This categorization necessitates an assessment of continuous data related to the degree of hypoxemia, as indicated by the partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspiratory oxygen concentration (FiO_2) ratio; these data were not at our disposal. However, fortunately, in this research, many essential comorbidities (>20) were recorded separately, thus reducing interpretation biases.

Personalized health care is a priority in the fight against the CARDS pandemic and should focus on analyzing the environment and the patient's risk. Lifestyle adjustments are mandatory for patients with multimorbidities before and after these respiratory infections since they affect predispositions and the potential for developing severe clinical infections. In addition, patients with clinical conditions can benefit from blood glucose management, smoking cessation, and monitoring of clinical conditions by a healthcare team.

Conclusion

Mortality from CARDS was higher among people with HDD and metabolic diseases, smoking, or neurological diseases concomitantly. In the case of metabolic diseases, despite the statistical findings, it is important to note the wide confidence interval and small sample size of people with metabolic diseases in this study. Thus, caution is needed in interpreting these morbidity data, because it could be a spurious finding that requires further investigation in future studies. Most patients with HDD who died were male and had three comorbidities.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

This study was approved by the Ethics Committee for Research with Human Beings of the Federal University of Maranhão (UFMA; Approval No. 4,227,396). The project appreciation meeting took place at UFMA on August 20, 2020.

Authors contributions

MFMA, LMB, and MSN conceived and designed the study, conducted the research, provided materials, and collected and organized the data.

TMA, CRST, ACPJC, and LMP analyzed and interpreted data and wrote the initial and final draft of the article.

FSS provided research materials and collected and organized data.

RAO and EAB analyzed and interpreted data and wrote the initial and final draft of the article.

MSS and LMP provided research materials and collected and organized the data.

MFMA and LMB conceived and designed the study, wrote the initial and final drafts, of the article, and provided logistic support.

All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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