Original Article

Association between COVID-19 and diabetes mellitus with intensive care unit care and need for mechanical ventilation: a retrospective cohort study of hospitalized patients in Southern Brazil

Associação entre COVID-19 e diabetes mellitus na unidade de terapia intensiva e a necessidade de ventilação mecânica: um estudo restrospectivo de coorte de pacientes hospitalizados no sul do Brasil

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ABSTRACT

Introduction: In late 2019, the coronavirus disease (COVID-19) emerged in Wuhan, China. COVID-19 was characterized in March 2020 as a pandemic and has already caused a million deaths worldwide. Studies help clarify the clinical profile of this disease, repeatedly showing that the presence of morbidities such as type 2 diabetes mellitus (DM2) and its associated diseases (obesity, hypertension, and cardiovascular disease) are important risk factors for the severity and prognosis of the disease, in addition to advanced age. Therefore, this study aimed to analyze the association between COVID-19 and DM2 and clinical outcomes and mortality in patients admitted to a hospital in the metropolitan region of Porto Alegre, Rio Grande do Sul, Brazil. **Methods:** In this cohort study, we retrospectively reviewed 501 hospitalized patients with COVID-19, with or without diabetes, who were admitted between April 2020 and October 2021. **Results:** Diabetic patients were significantly older and presented more hypertension and cardiovascular disease. The most common symptoms at the onset of the disease in general were dyspnea, followed by dry cough, fever, myalgia, and fatigue. The DM2 was a risk factor independently associated with the outcomes of intensive care unit (ICU) care (32% increase), mechanical ventilation (30% increase), and hemodialysis (91% increase). **Conclusions:** The study concluded that patients with COVID-19 and DM2 had a significantly higher risk of ICU admission and a greater need for mechanical ventilation and hemodialysis, but DM2 was not a risk factor for increased mortality.

RESUMO

Introdução: No final de 2019, a doença do coronavirus (COVID-19) emergiu em Wuhan, China. COVID-19 foi caracterizado em março de 2020 como uma pandemia, e já causou um milhão de mortes ao redor do mundo. Estudos ajudam a esclerecer o perfil clínico dessa doença, repetidamente demonstrando que a presença de comorbidades como diabetes mellitus tipo 2 (DM2) e doenças associadas (obesidade, hipertensão e doença cardiovascular) são fatores de risco importantes para a gravidade e prognóstico da doença, em adição à idade avançada. Dessa forma, este estudo objetiva analisar a associação entre COVID-19 e DM2 e os desfechos clínicos e mortalidade e pacientes admitidos em um hospital na região metropolitana em Porto Alegre, Rio Grande do Sul, Brasil. **Método:** Nesse estudo de coorte, nós revisamos, retrospectivamente, 501 pacientes hospitalizados com COVID-19, com ou sem diabetes, que foram admitidos entre abril de 2020 e outubro de 2021. **Resultados:** Pacientes diabéticos eram significativamente mais velhos e apresentavam mais hipertensão e doença cardiovascular. Os sintomas mais comuns no início da doença eram a dispneia, seguida por tosse seca, febre, mialgia e fatiga. A DM2 foi um fator de risco independente associada com desfechos de necessidade de cuidados em unidades de terapia intensiva (UTI) (aumento de 32%), ventilação mecânica (aumento de 30%) e hemodiálise (aumento de 91%). **Conclusão:** O estudo concluiu que pacientes com COVID-19 e DM2 têm um risco significativamente mais alto de serem admitidos na UTI e têm uma maior necessidade de ventilação mecânica e hemodiálise, mas a DM2 não foi associada a um fator de risco de maior mortalidade.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization on March 11th 2020, affecting millions of people worldwide[1].

Diabetes mellitus (DM) has been seen as a risk factor for COVID-19 since its inception[2]. People with DM are more susceptible to infections caused by bacteria, viruses, and fungi than individuals without DM, due to their relatively lower immune function[3-5]. Further, in DM, there is a low-grade inflammation state and in COVID-19, the degree of systemic inflammation is high, and this is perceived by elevations in inflammatory markers such as C-reactive protein (CRP) and ferritin[6]. Indeed, studies have repeatedly highlighted that the presence of morbidities such as DM, especially type 2 (DM2), and its associated diseases (obesity, hypertension, and cardiovascular disease) are important risk factors for the severity and prognosis of COVID-19, as many patients with DM and COVID-19 develop the most severe form of the disease[7,8]. For instance, COVID-19 patients with DM are more likely to use mechanical ventilation (MV), have a higher rate of admission to ICU, and a higher mortality[2]. This accumulated evidence causes great concern in countries with a high prevalence of DM, such as Brazil[7]. However, most studies have limitations, and questions remain about the specific risk factors (associated comorbidities and age) that determine different risks of infection, disease severity, and mortality rate[9-11].

Therefore, this study aimed to analyze the association between COVID-19 and DM2 and clinical outcomes and mortality in patients hospitalized in the metropolitan region of Porto Alegre, Rio Grande do Sul, Brazil.

METHODS

Study Design

This retrospective cohort study was conducted at a hospital in the metropolitan region of Porto Alegre, Rio Grande do Sul, Brazil. All adult patients (≥18 years old) hospitalized between April 2020 and October 2021 with laboratory-confirmed COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) were included in the analysis. Patients with respiratory diseases, such as asthma, chronic obstructive pulmonary disease, tuberculosis, Down's syndrome, pregnant or lactating were excluded.

The sample size calculation was performed in WinPEPI (Program for Epidemiologists for Windows) version 11.43, and was based on the study by Shang et al.[10]. Considering a significance level of 5%, power of 80%, and estimated mortality difference of 12% between patients with and without DM2, a minimum of 286 patients (143 in each group) were obtained.

From then on, patients were divided into cases (DM2) and controls (no DM2). The diagnosis of DM2 was considered when the patient had a previous diagnosis of the disease in the medical record.

To avoid confounding factors, in the control group, participants with blood glucose >126 mg/dL without a medical diagnosis of DM2 and, in both groups, patients with type 1 DM and with insufficient clinical information were also excluded.

Ethical Statement

This research was approved by the Ethics and Research Committee of the University of Vale do Rio dos Sinos on December 4, 2020, under reference n°40589720.6.0000.5344.

Data Collection

Clinical and laboratory data were extracted from patients' electronic medical records. Clinical information collected included age, sex, signs and symptoms, laboratory tests, e.g., complete blood count, creatinine, urea, CRP, activated partial thromboplastin time (KTTP), prothrombin time (PT), D-dimer and qualitative urine analysis, associated comorbidities, ICU admission, need for mechanical ventilation (MV) and/or non-invasive MV, O_2 support and complications such as hemodialysis, sepsis, and mortality. For prognostic evaluation, the results of the laboratory tests were defined as those at the beginning of hospitalization.

Statistical Analyses

Quantitative variables were described as means ± standard deviation or median and interquartile range. Categorical variables were described as absolute and relative frequencies.

The comparison of means was performed using the Student's t-test. In the case of skewed distribution, the Mann-Whitney test was applied. Pearson's chi-square test or Fisher's exact test was used to compare proportions.

The Poisson regression model was applied to control for confounding factors in evaluating the independent prediction of DM2 in the outcomes studied. The criterion for entering the multivariate model was that the variable had a p-value <0.10 in the bivariate analysis.

The adopted significance level was 5% ($p<0.05$) for a two-sided test, and the analyses were performed with SPSS version 21.0.

RESULTS

Patients Characteristics

Data from 501 patients diagnosed with COVID-19 were analyzed. The final composition of the sample, after applying the exclusion criteria, is shown in Figure 1.

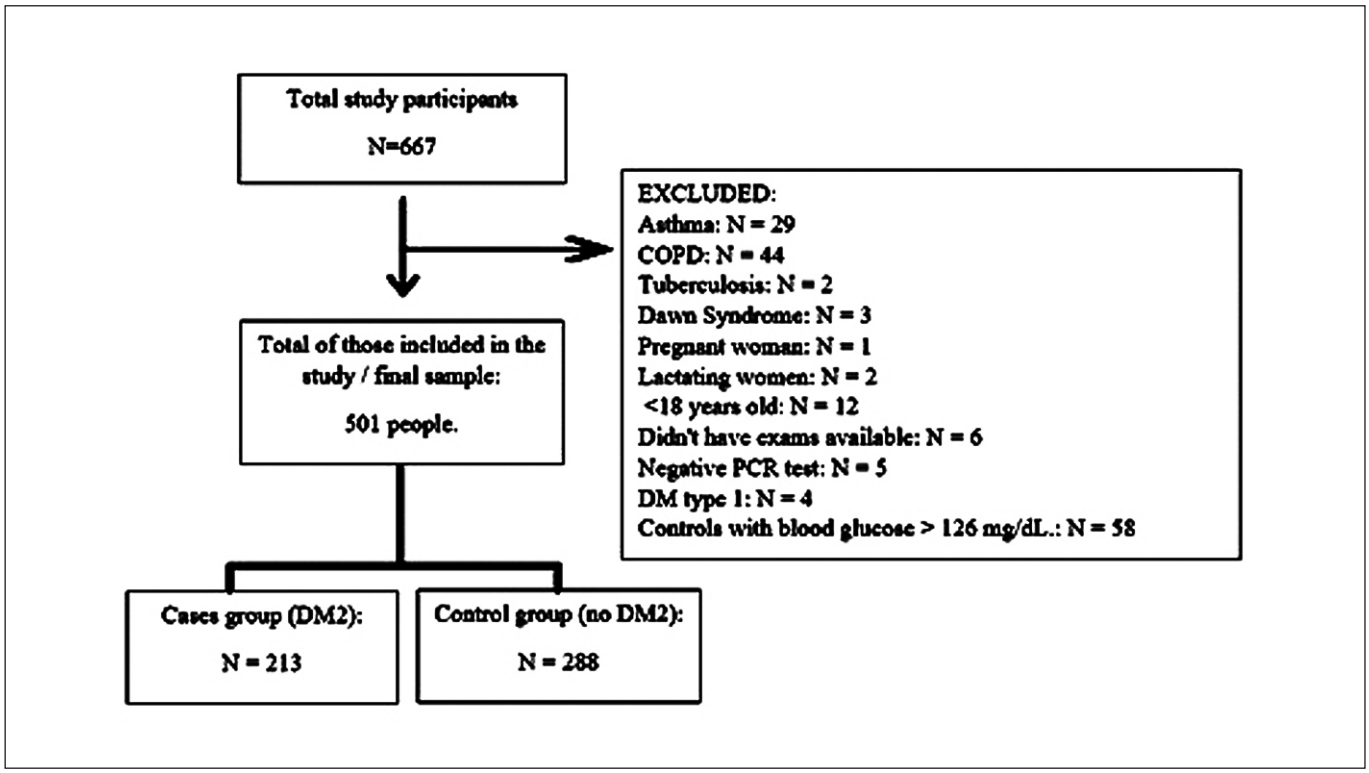

Figure 1 - *Flowchart of criteria for exclusion of patients from the study and final sample.*

The clinical characteristics of the patients are summarized in Table 1. Patients with DM2 were significantly older, presented more frequently with polypnea, vomit, hypertension and cardiovascular disease, and less frequently with dry cough, headache, ageusia and anosmia than patients without DM2.

Regarding biochemical tests (Table 2), patients with DM2 had lower levels of erythrocytes, hemoglobin, hematocrit, higher levels of creatinine, urea, D-dimer, positive glycosuria, and presence of ketone bodies in urine.

Impact of Diabetes Mellitus on Outcomes

When evaluating clinical outcomes (Table 3), patients with DM2 had a higher rate of ICU admission, used more MV and hemodialysis, had more sepsis, and a higher mortality rate.

The results of multivariate Poisson regression analysis are summarized in Table 4. Model 1 included more confounders but had a smaller sample size due to missing data in some variables. Using model 1, DM2 was a risk factor independently associated with ICU care, increasing the occurrence of this outcome by 65%. For model 2 (without variables with >10% missing data, but with a larger sample size), DM2 was a risk factor independently associated with the outcomes of ICU (32% increase in the occurrence of this outcome), MV use (30% increase), and the need for hemodialysis (91% increase).

Table 1 – Sociodemographic, clinical, and nutritional characteristics of the patients according to presence or absence of diabetes mellitus.

Variables	With DM (n=213; 42.5%)	Without DM (n=288; 57.5%)	P - value
Age (years)	64.3 ± 12.4	56.9 ± 17.7	<0.001
Gender			0.879
Man	116 (54.5)	160 (55.6)	
Woman	97 (45.5)	128 (44.4)	
Estimated weight (kg)	85.6 ± 23.3 (n=158)	86.5 ± 26.3 (n=182)	0.751
Estimated height (m)	1.68 ± 0.10 (n=155)	1.68 ± 0.10 (n=177)	0.775
Body mass index (kg/m^2)	30.2 ± 7.5 (n=155)	30.3 ± 7.9 (n=177)	0.868

Continuation Table 1 – Sociodemographic, clinical, and nutritional characteristics of the patients according to presence or absence of diabetes mellitus.

Variables	With DM (n=213; 42.5%)	Without DM (n=288; 57.5%)	P - value
Signs and Symptoms – n (%)			
Fever	64 (30.0)	108 (37.5)	0.101
Dyspnea	146 (68.5)	196 (68.1)	0.985
Polypnea	7 (3.3)	2 (0.7)	**0.041§**
Anorexia	25 (11.7)	30 (10.4)	0.747
Dry cough	74 (34.7)	128 (44.4)	**0.036**
Fatigue	46 (21.6)	80 (27.8)	0.141
Expectoration	8 (3.8)	6 (2.1)	0.396
Diarrhea	13 (6.1)	32 (11.1)	0.075
Myalgia	48 (22.5)	85 (29.5)	0.100
Nausea	15 (7.0)	20 (6.9)	1.000
Headache	27 (12.7)	57 (19.8)	**0.047**
Vomit	22 (10.3)	13 (4.5)	**0.019**
Pharyngalgia	10 (4.7)	23 (8.0)	0.198
Dysphagia	2 (0.9)	4 (1.4)	1.000§
Odynophagia	—	2 (0.7)	0.510§
Hypotension	3 (1.4)	3 (1.0)	0.703§
Ageusia	5 (2.3)	22 (7.6)	**0.017**
Anosmia	2 (0.9)	19 (6.6)	**0.004**
Comorbidities			
Hypertension	182 (85.4)	118 (41.0)	<0.001
Cardiovascular disease	46 (21.6)	35 (12.2)	0.007
Chronic kidney disease	13 (6.1)	8 (2.8)	0.107
Liver disease	3 (1.4)	5 (1.7)	1.000§
Immunosuppressed	2 (0.9)	2 (0.7)	1.000§
Cancer	5 (2.3)	12 (4.2)	0.389
Others	55 (25.8)	66 (22.9)	0.519

Results are expressed as mean ± standard deviation or as number of patients (column percentage). Statistical analyses were conducted using student's t-test for continuous variables and Pearson's chi-squared test or Fisher's exact test (§) for categorical variables. Values highlighted in bold signal association between categories.

Table 2 – Laboratory tests of patients at hospital admission according to presence or absence of type 2 diabetes mellitus.

Variables	With (n=213)	Without (n=288)	P - value
Red blood cells – average ± SD			
Erythrocyte	4.44 ± 0.67	4.55 ± 0.60	**0.043**
Hemoglobin	13.0 ± 2.0	13.4 ± 1.8	**0.007**
Hematocrit	38.0 ± 5.5	39.0 ± 5.2	**0.033**
Mean Corpuscular Volume	85.8 ± 5.5	85.7 ± 6.8	0.807
Mean Corpuscular Hemoglobin	29.3 ± 2.0	29.8 ± 4.0	**0.071**
MCHC	34.0 ± 1.9	34.4 ± 1.8	0.056
Red Cell Distribution Width	14.1 ± 1.5	13.9 ± 1.3	0.230
Platelets	233389 ± 89116	224087 ± 83037	0.503
Blood elements, absolute counts, median (IQR)			
Leucocytes	7600 (6100 - 10950)	8450 (6025-11075)	0.496
Neutrophils	6112 (4482-9448)	6405 (4382-9514)	0.615
Band neutrophils	0 (-)	0 (-)	0.383
Lymphocytes	935 (673-1369)	1005 (700-1428)	0.717
Monocytes	459 (288-688)	519 (329-726)	0.118
Eosinophils	0 (0-17.5)	0 (0-20)	0.522
Basophils	14 (8-28)	14 (9-28)	0.526

Continuation Table 2 – Laboratory tests of patients at hospital admission according to presence or absence of type 2 diabetes mellitus.

Variables	With (n=213)	Without (n=288)	P - value
Blood elements, as percentage, median (IQR)			
Neutrophils – average ± SD	78.2 ± 11.1	78.0 ± 11.7	0.827
Band neutrophil	0 (-)	0 (-)	0.411
Lymphocytes	12.2 (8.0-18.6)	11.8 (8.1-18.3)	0.684
Monocytes	5.6 (4.0-8.3)	5.9 (4.0-9.0)	0.491
Eosinophils	0 (0-0.2)	0 (0-0.2)	0.631
Basophils	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.749
Biochemistry – median (IQR)			
Creatinine	1.1 (0.8-1.6)	0.9 (0.7-1.2)	**<0.001**
Urea	48 (33-77)	37 (28-51)	**<0.001**
C-reactive protein	131.2 (69.9-209.8)	121.9 (76.6-188.9)	0.943
Coagulation			
APTT – average ± SD	27.7 ± 7.8 (n=170)	27.9 ± 7.2 (n=221)	0.886
PT (INR) – median (IQR)	1.07 (1.00-1.13) (n=182)	1.04 (1.00-1.13) (n=244)	0.325
D-Dimer – median (IQR)	1244 (754-2280) (n=139)	1016 (620-1759) (n=186)	**0.034**
Qualitative Urine Analysis			
Positive Proteinuria	36/122 (29.5)	46/136 (33.8)	0.542§
Proteinuria Level			0.127§
1	22 (61.1)	37 (80.4)	
2	11 (30.6)	6 (13.0)	
3	3 (8.3)	3 (6.5)	
Positive Glycosuria	66/122 (54.1)	14/135 (10.4)	**<0.001§**
Glycosuria Level			0.498§
1	12 (18.2)	3 (21.4)	
2	24 (36.4)	7 (50.0)	
3	30 (45.5)	4 (28.6)	
Positive Ketone Bodies	25/122 (20.5)	11/134 (8.2)	**0.008§**
Level of Ketone Bodies			0.451§
1	18 (75.0)	9 (81.8)	
2	3 (12.5)	2 (18.2)	
3	3 (12.5)	—	

MCHC = mean corpuscular hemoglobin concentration; APTT = activated partial thromboplastin time; PT = prothrombin time. Results are expressed as mean ± standard deviation or median [interquartile range] for continuous variables and as number of patients and (column percentage) for categorical variables. Statistical analysis by student's t-test or Mann-Whitney U test (§) for continuous variables and by Pearson's chi-squared test for categorical variables. Values highlighted in bold signal association between categories.

Table 3 – Outcomes and clinical complications of patients according to presence or absence of type 2 diabetes mellitus.

Variables	With (n=213)	Without (n=288)	P - value
Treatment in ICU	100 (46.9)	97 (33.7)	**0.004**
Mechanical ventilation	127 (59.6)	124 (43.1)	**<0.001**
Invasive mechanical ventilation	76 (35.7)	80 (27.8)	0.073
O_2 support	157 (73.7)	217 (75.3)	0.754
Clinical complications			
Hemodialysis	46 (21.6)	22 (7.6)	**<0.001**
Sepsis	30 (14.1)	18 (6.3)	**0.005**
Outcomes			**0.030**
Discharge	120 (56.3)	195 (67.7)	
Death	82 (38.5)	84 (29.2)	
Transfer	11 (5.2)	9 (3.1)	

ICU = intensive care unit. Results are expressed as number of patients and (column percentage). Statistical analysis by chi-square. Values highlighted in bold signal association between categories.

Table 4 – Associations between type 2 diabetes mellitus and outcomes, multivariate analysis.

	Model 1 (n=165)	P-value	Model 2 (n=493)	P-value
Management				
Treatment in ICU	1.65 (1.02-2.67)	0.043	1.32 (1.03-1.70)	**0.026**
Mechanical ventilation	1.13 (0.81-1.59)	0.471	1.30 (1.07-1.58)	**0.009**
Invasive mechanical ventilation	1.25 (0.67-2.35)	0.480	1.13 (0.85-1.52)	0.402
O_2 support	1.10 (0.90-1.35)	0.342	1.03 (0.91-1.16)	0.670
Clinical complications				
Hemodialysis	0.72 (0.24-2.16)	0.554	1.91 (1.13-3.25)	**0.016**
Sepsis	1.73 (0.48-6.25)	0.401	1.99 (0.97-4.07)	0.060
Death	0.72 (0.35-1.47)	0.368	1.11 (0.85-1.46)	0.433

IICU = intensive care unit. Results are expressed as odds ratio and (95% confidence interval) for presence vs. absence of type 2 diabetes mellitus. Statistical analysis by Poisson regression. Model 1: adjusted for age, polypnea, dry cough, diarrhea, headache, vomiting, ageusia, anosmia, hypertension, cardiovascular disease, EQU glycosuria, QUA Ketone bodies, hemoglobin, erythrocyte, hematocrit, MCH, MCHC, creatinine, urea, D-dimers; Model 2: adjusted for age, polypnea, dry cough, diarrhea, headache, vomiting, ageusia, anosmia, hypertension, cardiovascular disease, hemoglobin, erythrocyte, hematocrit, MCH, MCHC, creatinine, and urea. Values highlighted in bold signal association between categories.

DISCUSSION

From the multivariate Poisson regression, DM2 was found to be an independent risk factor associated with the need for ICU care and the use of MV, corroborating other studies published in the literature[12,13]. In a cohort study carried out in an ICU, among patients who required MV, 26% had DM, the second comorbidity with the greatest impact, second only to obesity[14]. Other studies have also shown that patients with DM and COVID-19 have significantly higher rates of ICU admission, greater need for MV, and renal complications[15,16]. Acute kidney injury has been shown to be a serious complication of COVID-19 disease, but its cause remains unclear. Direct cytopathological damage, cytokine/septic storms, drug toxicity, and dehydration may be potential causes of kidney injury in these patients[17]. In our study, the need for hemodialysis was a significantly more present outcome in the DM2 group. Studies have highlighted that DM is a significant factor in the mortality rate of patients with COVID-19 on hemodialysis[18]. Another retrospective study identified that the incidence of acute kidney injury was more frequent among patients with CKD and DM, with comorbidities associated with greater vulnerability to kidney injury. The same authors also observed that patients with severe acute respiratory syndrome who required MV had a higher rate of acute renal failure than those who did not require MV[17].

Several studies have shown that since the beginning of the pandemic, DM2 has been a risk factor for mortality[9-11]. However, this result was not found in the present study. Mortality in the DM2 group was higher (38.5% vs. 29.2%), but the difference was not strong enough to support that DM2 is an independent risk factor for mortality. A previous study by Al-Salameh et al.[19], in France, which included 433 patients with COVID-19, 115 (26.6%) of whom had DM, demonstrated that DM was not associated with mortality, but was associated with ICU admission, consistent with the findings of the present study. In a study in Belgium, Orioli et al.[20] found no significant differences in mortality rates when comparing the short-term prognosis of COVID-19 patients with and without FM.

Han et al.[21] performed a meta-analysis to clarify the effects of anti-inflammatory and antidiabetic agents in COVID-19 patients with DM. The authors showed that the use of metformin was associated with significantly lower mortality and a poorer prognosis in patients with DM and COVID-19. Another meta-analysis conducted by Nguyen et al.[22] also associated metformin and other drugs with a lower mortality rate in COVID-19 patients with DM2. The meta-analysis conducted by Prattichizzo et al.[23] aimed to evaluate the impact of HbA1c values pre-admission or at hospital admission on mortality or worsening in patients with COVID-19 and DM2. The results indicated that patients with DM and poor glycemic control before infection may have an increased risk of COVID-19-related mortality. Unfortunately, it was not possible to evaluate this association due to the lack of information on the medications used by the patients in the medical records.

Kastora et al.[24] conducted a systematic review and meta-analysis to evaluate collective and geographically stratified mortality, ICU admission, ventilator requirements, severity of disease, and discharge rate among patients with COVID-19 and diabetes. To our knowledge, this is the first study to evaluate the outcomes of patients with diabetes in the context of COVID-19, considering the geographic location. The results showed that patients with diabetes had a higher risk of negative clinical outcomes during hospitalization. Although many studies from the Far East and the Middle East reported significantly higher mortality in patients with diabetes, these findings were not found in studies from the European Union and American regions. The authors pointed out that this variability in data may be related to inequalities in access to health care and affordable antidiabetic drugs or inherent

non-modifiable (genetic variants) and modifiable (obesity) parameters among the ethnic groups studied. The same study also reinforced that patients with better glycemic control and using oral medications to reduce glucose levels, such as metformin, had significantly better results in terms of mortality.

Our research also showed that the group of diabetic patients was composed of significantly older individuals corroborating what was found in other studies[9,10]. Previous studies have already shown that aging is a risk factor that contributes to a worse prognosis of COVID-19[25,26].

The prevalence of hypertension in the overall sample of our study was 59.9%. It was present in 85.4% of patients with DM2 and 41% without diabetes. Hypertension was the most prevalent comorbidity, followed by DM2 (42.5%) and cardiovascular disease (16.17%). The study by Liu et al.[27] also found hypertension as the most common comorbidity (49.5%) in patients with COVID-19, followed by diabetes (24.8%) and cardiovascular disease (21.8%), corroborating our data. Wang et al.[28], in a meta-analysis, showed that hypertension and diabetes are risk factors for a worse prognosis in patients with COVID-19.

A meta-analysis, which aimed to evaluate the effect of coagulation indicators, such as D-dimers and inflammatory biomarkers, such as CRP, in patients with COVID-19, showed that diabetic patients had higher levels of CRP than nondiabetic patients, correlating this finding with inflammatory reactions and related tissue destruction. The authors also noted that the concentration of D-dimer in diabetic patients was significantly higher than in nondiabetic patients[29]. Similar findings were found by Miri et al.[30]. These results partially corroborate the results of the present study since a significant difference was observed only in D-dimer levels (p=0.034).

The increased levels of creatinine and urea in the DM2 group were consistent with the study by Zhang et al.[11]. However, different results were also found by Shang et al.[10].

Positive glycosuria and the presence of ketone bodies in the urine (p=0.008) were common findings in diabetic patients, especially in those without glucose control. When the threshold for renal reabsorption of glucose is exceeded (serum glucose level equal to approximately 160 mg/dL), the passage of glucose into the urine of the patient begins. Ketone bodies that appear in the urine indicate the use of lipid and protein reserves in the body of patients with diabetes due to the inability to use glucose as an energy source[31].

This study has some limitations. First, it was a retrospective study. Data for blood glucose monitoring were not available in the medical records. Therefore, the impact of glycemic control could not be assessed. HbA1c values, the gold standard test for diagnosing DM2, were not available. There was no information on the medications used by the patients in the medical records. Obesity is known to play an important role in COVID-19 outcomes. However, weight and height data were only available for a limited number of patients, so the impact of obesity could not be observed.

CONCLUSION

Patients with COVID-19 and DM2 had a significantly higher risk of ICU admission and a greater need for MV and hemodialysis than patients without DM2. Conversely, DM2 was not a risk factor for increased mortality. The results of our study emphasize the need for further investigation of the pathogenic mechanism of the relationship between diabetes and COVID-19 to aid in therapeutic management.

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