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Outcomes of Hospitalized Patients with Type 2 Diabetes and COVID-19: The Impact of Glycaemic Control

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A B S T R A C T

Introduction: Diabetes mellitus is associated with poorer outcomes in patients with coronavirus disease (COVID-19). The mechanisms for this association are not fully elucidated. We aimed to evaluate the clinical characteristics and outcomes of hospitalized patients with type 2 diabetes (T2DM) and COVID-19, as well as the impact of blood glucose control on mortality.
Material and Methods: In this retrospective study, we included 97 patients (38 with T2DM, 59 without diabetes). We compared demographic characteristics, comorbidities, admission findings and outcomes between patients with and without diabetes. To assess glycaemic control, individual derived time in range (70-180 mg/dL) was derived as the proportion of values within range. Derived time above range was calculated as the proportion of values above range.
Results: The fatality rate of patients with diabetes was 36.8%. Among these patients, nonsurvivors presented with higher Pneumonia Severity Index score (159 ±36 *vs* 109±30, *p*=0.001), a higher N-terminal brain natriuretic peptide (5521 [4256-15280] *vs* 1541 [288-2349] pg/mL, *p*=0.047), a lower PaO2/FiO2 ratio (214 [181-259] *vs* 300 [248-347], *p*=0.033) and were more likely to have bilateral lung involvement at admission (78.6% *vs* 29.2%, *p*=0.013). Rates of acute kidney injury (85.7% *vs* 33.3%, *p*=0.003), acute heart failure (57.1% *vs* 25.0%, *p*=0.048) and secondary bacterial infection (64.3 *vs* 26.1%, *p*=0.022) were higher in deceased patients. Nonsurvivors had a lower derived time in range (38% *vs* 73%, *p*=0.020) and a higher derived time above range (62% *vs* 27%, *p*=0.020).
Conclusion: A poorer glucose control assessed by lower derived time in range during hospitalization was associated with in-hospital death.

Palavras-chave:
Controlo Glicémico;
COVID-19;
Diabetes Mellitus Tipo 2.

Resultados Clínicos de Doentes Hospitalizados com Diabetes Tipo 2 e COVID-19: O Impacto do Controlo Glicémico

R E S U M O

Introdução: A diabetes *mellitus* é um dos fatores associados a pior prognóstico na doença por coronavírus-19 (COVID-19). Os mecanismos desta associação não estão ainda totalmente esclarecidos. O objetivo deste trabalho foi avaliar as características clínicas de doentes hospitalizados com diabetes *mellitus* tipo 2 (DMT2) e COVID-19, assim como o impacto do controlo glicémico na mortalidade.
Material e Métodos: Neste estudo retrospetivo foram incluídos 97 doentes (38 com DMT2, 59 sem diabetes). Foram comparadas características demográficas, comorbilidades, dados clínicos à admissão hospitalar, complicações e mortalidade entre doentes com e sem diabetes. Para avaliar o controlo glicémico, o tempo no alvo foi derivado como a proporção de valores de glicose capilar dentro do alvo terapêutico (70-180 mg/dL). O tempo acima do alvo foi calculado como a proporção de valores acima do alvo.

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Resultados: A taxa de mortalidade de doentes com diabetes foi de 36,8%. Entre estes, os falecidos apresentaram-se com maior índice de gravidade de pneumonia (159 ±36 *vs* 109±30, *p*=0,001), valor de NT-proBNP (fração N-terminal do péptido natriurético tipo B) superior (5521 [4256-15280] *vs* 1541 [288-2349] pg/mL, *p*=0,047), rácio PaO2/FiO2 inferior (214 [181-259] *vs* 300 [248-347], *p*=0,033) e maior envolvimento pulmonar bilateral à admissão (78,6% *vs* 29,2%, *p*=0,013). Durante o internamento, desenvolveram com maior frequência lesão renal aguda (85,7% *vs* 33,3%, *p*=0,003), insuficiência cardíaca aguda (57,1% *vs* 25,0%, *p*=0,048) e sobreinfecção bacteriana (64,3 *vs* 26,1%, *p*=0,022). Os doentes falecidos apresentaram também menor tempo no alvo (38% *vs* 73%, *p*=0,020) e maior tempo acima do alvo (62% *vs* 27%, *p*=0,020).
Conclusão: Um mau controlo glicémico avaliado através de um menor tempo no alvo durante o período de internamento pode estar associado a maior mortalidade intra-hospitalar

Introduction

Coronavirus 2019 disease (COVID-19) has recently emerged as a rapidly spreading disease, affecting more than 100 countries worldwide, reaching pandemic proportions. Since 31 December 2019, more than 519 million cases of COVID-19 have been reported, including more than 6,2 million deaths.[1] The severity of the disease ranges from an asymptomatic condition or mild illness to severe pneumonia culminating in respiratory failure and death. Severe cases occur mostly in susceptible patients with comorbidities.[2]

Type 2 diabetes (T2DM) is one of the most prevalent comorbidities described in COVID-19 patients, leading to more severe disease and higher mortality in studies published to date.[2–5] Diabetic patients are known to have an increased risk of developing and dying from infectious diseases.[6,7] In previous coronaviral epidemics, diabetes and hyperglycaemia were independent predictors for death and morbidity in infected patients.[8,9]

Despite the increasing evidence that diabetes is associated with poor COVID-19 outcomes, the pathophysiological mechanisms behind this association are not fully explained. There is also a lack of studies directed at in-hospital glycaemic control among patients with diabetes and COVID-19. The limited previous evidence showed that poorly-controlled hyperglycaemia increased the severity and mortality in patients with COVID-19.[4,10–12]

In this study, we aimed to describe the demographic, clinical and outcome characteristics of hospitalized patients with COVID-19 and T2DM, compared with a population of non-diabetic patients. We also evaluated risk factors for a worse outcome among diabetic patients, and analysed the impact of glucose lowering drugs and in-hospital glucose control on prognosis.

Material and Methods

Study Design

This was a retrospective cohort study conducted in Portugal. Consecutive inpatients with laboratory-confirmed SARS-CoV-2 infection admitted to the hospital between 25 March 2020 and 25 May 2020 were included in our study. Patients transferred from other services/institutions, with a primary diagnosis other than COVID-19 or admitted to an intensive care unit were excluded from our study. We also excluded patients with other types of diabetes rather than T2DM. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by our institutional review board.

Data abstraction

We collected data from medical records of patients, including age, sex, functional status, whether or not living in a nursing home residency, history of diabetes, other comorbidities (hypertension, chronic pulmonary disease, chronic kidney disease) and chronic medication (glucose-lowering drugs and renin–angiotensin–aldosterone system [RAAS] inhibitors). We also recorded laboratory, radiological and clinical parameters on admission, such as c-reactive protein (CRP), n-terminal pro-b-type natriuretic peptide (NT-proBNP), partial arterial pressure of oxygen (PaO2), fraction of inspired oxygen (FiO2), PaO2/FiO2 ratio, chest radiography (bilateral/unilateral lesions) and all the necessary parameters for the calculation of Pneumonia Severity Index (PSI) Score[13] (age, sex, nursing home resident, neoplastic disease, liver disease history, chronic heart failure (CHF) history, cerebrovascular disease history, renal disease history, altered mental status, respiratory rate, systolic blood pressure, temperature, pulse, pH, urea, sodium, glucose, haematocrit, PaO2 and effusion on x-ray); adverse outcomes (acute heart failure [AHF], acute kidney injury [AKI] and secondary bacterial infections); treatments (hydroxychloroquine [HCQ], azithromycin [AZ], corticosteroids [CS], supplemental oxygen, non-invasive ventilation [NIV]); date of admission and date of discharge or death. All data were obtained using the electronic medical record systems in the hospital using a standardized data collection form and there was duplicated data extraction (two investigators working independently).

Definitions and measurements

The diagnosis of COVID-19 was performed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2. Patients were identified as having diabetes mellitus if they were currently treated with insulin or oral antihyperglycemic agents, or with previous known history of diabetes, or if they met the most recent diagnostic criteria of diabetes of the World Health Organization.[14] The functional status (as a measurement of the patient's ability to perform activities of daily living independently) was assessed by Katz Index of Independence in Activities of Daily Living (ADL),[15] with a scale ranging from 0 to 6 (6 indicating full function). Patients with an index of 3 or less were considered as having moderate or total impairment of functionality. Pneumonia severity at admission was assessed according to the PSI Score (Pneumonia Severity Index), which provides a risk stratification of community acquired pneumonia. AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes definition.[16]

To assess glycaemic control during hospital stay, all blood glucose levels were recorded for each diabetic patient in the first seven days. In our unit diabetic patients had four capillary blood glucose tests per day (a fasting test, before lunch, before dinner and 3 hours after dinner). Individual time in range (percentage of time with plasma glucose between 70-180 mg/dL) was derived as the proportion of values within range (Derived TIR). TAR (time above range) was derived as the proportion of values above range, and TBR (time below range) as the proportion of values below range.

For the purpose of presenting more data on glucose variability, we used a freely available Web-based application for rapid computation of numerous glucose variability parameters from CGM (continuous glucose monitoring) data: "GlyCulator – version 2.0" (calculates every metric of CGM data recommended by the International Consensus).[17] We therefore obtained data on standard of deviation (SD), coefficient of variation (CV), low and high blood glucose indexes (LBGI and HBGI), M-100 index (weighted average of glucose values - provides a measure of stability of glycemia in comparison with an arbitrary assigned "ideal" glucose value, "R," set to 100 mg/dL) and J-index (a measure of quality of glycaemic control based on the combination of information from the mean and SD calculated as 0.001 × [mean + SD]).

Statistical analysis

Categorical variables were presented according to frequencies and percentages. All continuous variables were tested for normality by Sminorv-Kolmogorov test. Data showing normal distribution were expressed as mean and standard deviation, and the remaining as median and interquartile range (IQR). Pearson's chi-square, T-student, Mann-Whitney-U and Fisher's exact tests were used to compare patients with and without diabetes, and between non-survivors and survivors, as appropriate. Statistical analysis was performed using SPSS Statistics software (version 26). The level of significance was assigned at a p value < 0.05.

Results

Baseline characteristics of COVID-19 infected patients

The patients' characteristics are summarized in Table 1. Of 97 COVID-19 patients, 38 patients had T2DM (39.2%) and 59 were non-diabetic patients (60.8%). In the group of diabetic patients, 34 had a diagnosis of T2DM already established prior to admission and four patients were diagnosed with T2DM on admission [two patients presented with hyperosmolar hyperglycaemic syndrome, two were asymptomatic patients with HbA1c > 6.5 % (48 mmol/mol)].

The sex distribution and functional status was similar between groups. The mean age was 75 [±15] and 80 [±9] years in the group without DM and with T2DM, respectively (p=0.061). Patients with T2DM were more likely to be nursing home residents (55.3% *vs* 33.9%, p=0.038). A higher prevalence of arterial hypertension (92.1% *vs* 59.3%, p=0.001), previous medication with RAAS inhibitors (64.9% *vs* 44.1%, p=0.047), chronic heart failure (55.3% *vs* 32.2%, p=0.024) and chronic pulmonary disease (28.9% *vs* 11.9%, p=0.035) was observed in patients with diabetes (Table 1).

Status on admission

There were no significant differences regarding laboratory and radiologic findings at admission between the two groups of patients (Table 1).

Outcomes

The overall in-hospital fatality rate was 30.9%. The incidence of acute heart failure (36.8% *vs* 25.4%, p=0.230), acute kidney injury (52.6% *vs* 37.3%, p=0.137), bacterial secondary infection (40.5% *vs* 34.5%, p=0.551); hospital length of stay (10 [5-17] *vs* 10 [5-118] days, p=0.793), fatality rate (36.8% *vs* 27.1%, p=0.312), oxygen therapy or need for NIV (10.5% *vs* 5.4%, p=0.427) did not differ between the two groups of patients (Table 1).

Clinical characteristics of diabetic patients and outcomes

Among patients with T2DM who died compared with sur-

Table 1. Characteristics, laboratory findings, complications, treatments and outcomes of COVID-19 patients with and without type 2 diabetes.

	Non-DM (n=59)	T2DM (n=38)	*p*-value
Sex - female, n [%]	30 [50.8%]	21 [55.3%]	*0.671*
Age (years), mean [±SD]	75 [±15]	80 [±9]	*0.061*
Moderate or total impairment of functionality, n [%]	33 [55.9%]	25 [65.8%]	*0.334*
Nursing home resident, n [%]	20 [33.9%]	21 [55.3%]	*0.038*
Comorbidities			
Arterial Hypertension, n [%]	35 [59.3%]	35 [92.1%]	*0.001*
Chronic kidney disease, n [%]	14 [27.3%]	14 [36.8%]	*0.164*
Chronic Heart Failure, n [%]	19 [32.2%]	21 [55.3%]	*0.024*
Chronic pulmonary disease, n [%]	7 [11.9%]	11 [28.9%]	*0.035*
RAAS inhibitors previous treatment, n [%]	26 [44.1%]	24 [64.9%]	*0.047*
Admission findings			
PaO2/FiO2 ratio (mmHg), median [IQR]	280 [252-319]	258 [196-333]	*0.357*
PSI Score (points), mean [±SD]	115 [±46]	127 [±40]	*0.190*
NT-proBNP (pg/mL), median [IQR]	1677 [331-6530]	2274 [691-10103]	*0.517*
CRP (mg/L), median [IQR]	90 [55-175]	63 [26-128]	*0.135*
Bilateral lung involvement images, n [%]	29 [59.2 %]	18 [69.2%]	*0.392*
Non-invasive Ventilation, n [%]	3 [5.4%]	4 [10.5%]	*0.427*
Outcomes			
Acute heart failure, n [%]	15 [25.4 %]	14 [36.8%]	*0.230*
Acute kidney injury, n [%]	22 [37.3%]	20 [52.6%]	*0.137*
Bacterial secondary infection, n [%]	20 [34.5%]	15 [40.5%]	*0.551*
Death, n [%]	16 [27.1%]	14 [36.8%]	*0.312*
Hospital length of stay (days), median [IQR]	10 [5-18]	10 [5-17]	0.793

T2DM, type 2 diabetes mellitus; IQR, Interquartile range; RAAS inhibitors, renin–angiotensin–aldosterone system inhibitors; PaO2 arterial pressure O2; FiO2, fraction of inspired air; CRP, C-reactive protein; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PSI Score, Pneumonia Severity Index Score;.

Table 2. Characteristics, laboratory findings, complications, treatments and outcomes of deceased and surviving diabetic patients.

	Non-survivors (N=14)	Survivors (N=24)	*p*-value
Sex - female, n [%]	9 [64.3%]	12 [50%]	*0.506*
Age (years), mean [±SD]	80 [± 9]	77 [± 8]	*0.075*
Moderate or total impairment of functionality, n [%]	9 [64.3%]	16 [66.7%]	*0.850*
Nursing home resident, n [%]	9 [64.3%]	12 [50%]	*0.506*
Comorbidities			
Arterial Hypertension, n [%]	13 [92.9%]	22 [91.7%]	*0.896*
Chronic Kidney Disease, n [%]	5 [35.7%]	9 [37.5%]	*0.382*
Chronic Heart failure, n [%]	10 [71.4%]	11 [45.8%]	*0.126*
Chronic Pulmonary disease, n [%]	5 [35.7%]	6 [25.0%]	*0.482*
Admission findings			
PaO2/FiO2 ratio (mmHg), median [IQR]	214 [181-259]	300 [248-347]	*0.030*
PSI score (points), mean [±SD]	159 [± 36]	109 [± 30]	*0.001*
NT-ProBNP (pg/mL), median [IQR]	5521 [4256-15280]	1541 [288-2349]	*0.047*
CRP (mg/L), median [IQR]	61 [41-16]	63 [18-128]	*0.393*
Bilateral lung involved images, n [%]	11 [78.6%]	7 [29.2%]	*0.013*
Outcomes			
Acute heart failure, n [%]	8 [57.1%]	6 [25.0%]	*0.048*
Acute kidney injury, n [%]	12 [85.7%]	8 [33.3%]	*0.003*
Bacterial secondary infection, n [%]	9 [64.3%]	6 [26.1%]	*0.022*
Treatments			
AZ, n [%]	6 [42.9%]	2 [8.3%]	*0.010*
HCQ, n [%]	4 [28.6%]	24 [100%]	*0.029*
CS, n [%]	1 [7.1%]	4 [16,6%]	*0.587*
AZ + CS, n [%]	3 [21.4%]	0 [0%]	*0.032*
HCQ + CS, n [%]	2 [14.3%]	3 [12.5%]	*0.660*
HCQ + AZ, n [%]	7 [50%]	16 [66.7%]	*0.953*
HCQ + AZ + CS, n [%]	5 [35.7%]	2 [8.3%]	*0.029*
Supplemental oxygen, n [%]	14 [100%]	17 [70.8%]	*0.025*
Non-invasive Ventilation, n [%]	4 [28.6%]	0 [0%]	*0.014*

IQR, interquartile range; PaO2 arterial pressure O2; FiO2, fraction of inspired air; CRP, C-reactive protein; NT-proBNP, N-terminal-pro–B-type natriuretic peptide; PSI Score, Pneumonia Severity Index.

vivors, the former presented at admission with a higher PSI score (159 [±36] *vs* 109 [±30] points, *p*=0.001), a higher value of NT-proBNP (5521 [4256-15280] *vs* 1541 [288-2349] pg/mL, *p*=0.047), a lower PaO2/FiO2 ratio (214 [181-259] *vs* 300 [248-347], *p*=0.033) and were more likely to have bilateral involvement of lungs (78.6% *vs* 29.2%, *p*=0.013). In relation to complications during hospitalization, nonsurvivors were more likely to develop acute kidney injury (85.7% *vs* 33.3%, *p*=0.003), acute heart failure (57.1% *vs* 25.0%, *p*=0.048) and secondary bacterial infection (64.3% *vs* 26.1%, *p*=0.022) (Table 2).

Regarding treatment, T2DM patients who died were more often in need of supplemental oxygen (100% *vs* 70.8%, *p*=0.025) and NIV (28.6% *vs* 0%, *p*=0.014). Diabetic patients treated with azithromycin (AZ alone or AZ plus CS or AZ plus CS and HCQ) had a higher rate of fatality (Table 2). Patients treated with hydroxychloroquine alone had a higher rate of survival (*p*=0.029).

Chronic therapy and outcomes in diabetic patients

Among the 38 T2DM patients, 34 were chronically treated with one or more glucose-lowering drugs including: insulin (44.1% [n=15]), metformin (44.1% [n=15]), dipeptidyl peptidase-4 inhibitors (DDP4i) (35.3%% [n=12]), sodium-glucose co-transporter-2 inhibitors (SGLT2i) (8.8% [n=3]), glucagon-like peptide-1 receptor agonists (GLP1a) (5.9% [n=2]) and sulfonylureas (5.9% [n=2]).

When comparing deceased patients with survivors, there were no differences on the likelihood of being treated with insulin (60% *vs* 37.5%, *p*=0.269), metformin (50% *vs* 41%, *p*=0.730), and DDP4i (40 *vs* 33.3%, *p*=0.775). Only four patients were previously treated with SGLT2i or GLP1a, though none of these patients died. T2DM patients were more likely to develop AKI if they were under an insulin regimen (73.3 *vs* 26.7%, *p*=0.022), although when comparing with metformin-treated patients this association was not significant (OR 1.75 [0.740-4.139]). Most of insulin-treated patients had a previous CKD diagnosis (53.3%). Patients previously treated with metformin had lower acute heart failure rates than patients that were not (*p*=0.012). None of the patients treated with SGLT2i or GLP1a had acute cardiac injury (these patients were also under combined treatment with metformin).

Blood glucose levels and mortality in diabetic patients

All patients were treated with basal plus bolus correction insulin regimen. The median TIR for all T2DM patients was 49%, and the TAR was 52%. Nonsurvivors were more likely to have a lower TIR (38% *vs* 73%, *p*=0.020) and a higher TAR (62% *vs* 27%, *p*=0.020) (Fig. 1). TIR was higher than >70% for 36.8% of the patients. Survivors were more likely to have TIR higher than 70% (50% *vs* 14.3%, *p*=0.030) (Table 3).

Considering data estimates of glycaemic variability from Glycalculator, there were no differences between groups regarding HBGI (13.78 [7.09-21.89] *vs* 9.73 [3.35-17.03], *p*=0.151), M-100 index (297.41[194.23-386.75] *vs* 216.94 [147.00-321.54], *p*=0.123) and J-index (73.20 [45.82-104.39] – 56.99 [31.05-88.34], *p*=0.221) (Table 3).

Table 2. Glycaemic Control Measures of patients with type 2 diabetes.

	Nonsurvivors (N=14)	Survivors (N=24)	Total (N=38)	*p*-value
TBR (%)	0 [0-0]	0 [0-0]	0 [0-0]	*0.948*
TIR (%)	38 [17-58]	73 [41-82]	49 [21-78]	*0.020*
TAR > 180 (%)	62 [43-83]	27 [17-56]	52 [23-79]	*0.020*
TAR > 250 (%)	28 [25-45]	11 [0-43]	15 [0-42]	*0.379*
TIR> 70% (%)	2 [14.3%]	12 [50%]	14 [36.8%]	*0.030*
GlyCulator Data				
Glucose SD (mg/dL)	50.97 [33.05-94.72]	47.84 [34.02-83.23]	47.84 [34.02-83.23]	*0.851*
Glucose CV (%)	23.26 [17.46-35.76]	29.15 [19.63-37.84]	28.61 [18.83-36.23]	*0.526*
LBGI	0.11 [0.00-0.69]	0.08 [0.00-0.51]	0.08 [0.00-0.51]	*0.797*
HBGI	13.78 [7.09-21.89]	9.73 [3.35-17.03]	10.58 [4.40-20.16]	*0.151*
M-100 index	297.41 [194.23-386.75]	216.94 [147.00-321.54]	267.69 [158.90-342.52]	*0.123*
J-index	73.20 [45.82-104.39]	56.99 [31.05-88.34]	62.83 [35.03-88.34]	*0.221*

All continuous data are presented with median [IQR]; TBR, time below range (%); TIR, time in range (%); TAR, time above range (%); SD, standard of deviation; CV, coefficient of variation; LBGI, low blood glucose index; HBGI, high blood glucose index; M-100 index (measure of stability of glycemia in comparison with an arbitrary assigned "ideal" glucose value, "R," set to 100 mg/dl); J-index (a measure of quality of glycaemic control based on the combination of information from the mean and SD calculated as 0.001 × [mean + SD])..

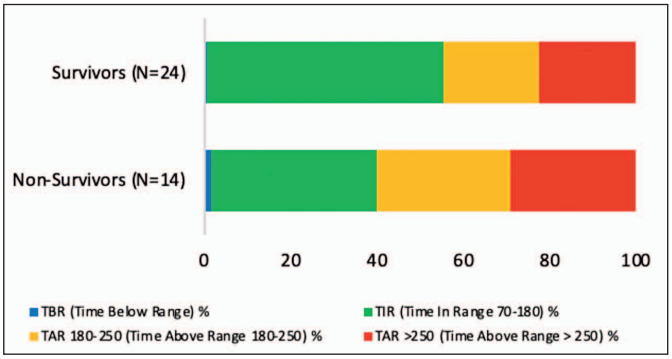

Figure 1. Glycemic control of type 2 diabetic patients infected with COVID-19. Data presentation as an AGP report. Comparison between survivors and nonsurvivors. TBR, time below range (%); TIR, Time in range (%); TAR, Time above range (%).

Discussion

In this retrospective study, we compare the outcomes of COVID-19 hospitalized patients with and without T2DM. Based on data from 97 patients with COVID-19, we found that the overall fatality rate was 30.9%. Several studies have considered older age as a risk factor of poor prognosis in COVID-19 patients and a fatality ratio of 22% was observed in Chinese patients aged above 80 years.[18,19] Moreover, the number of comorbidities also correlates with worse prognosis.[2] Our high fatality rate can therefore be possibly explained by the population characteristics, comprising a high percentage of elderly patients with functional impairment and comorbidities.

In published data so far,[3,4,19] diabetic patients were more likely to have a worse outcome. However, we could not find this association in our study. Our study population was aged, and the overall prevalence of arterial hypertension was 72%. One possible explanation for this result is that the presence of older age and hypertension may attenuate the association of T2DM with poor outcome, as described by Huang *et al* in a meta-analysis. These authors showed in a meta-regression that the association between diabetes and poor outcome was influenced by age and hypertension, and that the effect estimate of diabetes was less in older and hypertensive patients. It was hypothesized that this effect might be explained by differences in ACE2 levels and RAS signalling in older and hypertensive individuals (lower ACE2 levels but a higher RAS signalling, resulting in a potentially decreased susceptibility to the disease, but a greater severity).[20]

Although it was beyond the purpose of our study, we found that diabetic patients who died were more often treated with azithromycin. Azithromycin treated patients were also the ones with secondary bacterial infections, carrying a higher risk of mortality.

Our findings were therefore influenced by this confounder and are contradictory to what has been reported in the literature, as azithromycin has only been associated with increased mortality if combined with hydroxychloroquine.[21–23]

When considering chronic medication prior to admission, we found no association between glucose-lowering drugs and fatality rate. In the CORONADO study the authors analysed the phenotypic characteristics of 1317 diabetics infected with COVID-19 and also found no association between glucose-lowering drugs, including DPP-4 inhibitors and COVID-19 prognosis.[24] Insulin-treated patients were more likely to suffer AKI and metformin, SGLT2i or GLP1ra-treated patients had lower acute heart failure rates. Chen Y *et al* reported the outcomes of diabetic patients in association with glucose lowering medications and revealed that insulin users showed worse clinical outcomes (disease progression or death) than those who did not use insulin.[25] Probably, patients under insulin may have some degree of renal impairment (contraindicating some oral glucose-lowering drugs), which may explain this association with mortality.

Non-survivors were more likely to have a higher TAR and a lower TIR, reflecting an association between poor glucose control and mortality, which is consistent with the available literature.[4,10,24,26–29] A recent retrospective study that included 952 T2DM COVID-19 patients published by Zhu *et al* also indicated that poor glycaemic control was associated with worse outcomes.[4] Bode *et al* reported that COVID-19 patients with diabetes and/or uncontrolled hyperglycaemia had a longer length of stay and markedly higher mortality than patients without.[10] Another retrospective study of 269 severe COVID-19 cases showed that hyperglycaemia during hospitalization was a risk factor for death.[29]

Hyperglycaemia may lead to severe COVID-19 and death by exacerbating itself an inflammatory response. Sardu and colleagues divided 59 COVID-19 patients into hyperglycaemic and normoglycemic groups, observing that patients with hyperglycaemia presented higher IL-6 levels at admission and during hospitalization along with higher levels of D-dimer.[27] Zhu *et al* also found that patients with COVID-19 with diabetes with an in-hospital median

blood glucose concentration of less than 6.4 mmol/L (115.2 mg/dL) had lower rates of lymphopenia, neutrophilia, increases in CRP, and procalcitonin than patients with a median blood glucose concentration of 7.5 mmol/L (135 mg/dL) or higher.[4] Hyperglycaemia impairs different components of the host response, including cytokines regulation and immune cells function.[30,31] Among patients with COVID-19, those with diabetes are more susceptible to the detrimental effect of the cytokine storm.[32]

There are several limitations in our study. Firstly, it took place during an emergency outbreak, when the healthcare system was overwhelmed, therefore we lack a matched control to compare patient groups. Secondly, our sample has a small number of COVID-19 patients with diabetes, which impaired further regression statistical analyses to adjust for confounders and possibly made it impossible for some results to reach statistical significance. Thirdly, medical records of patient's weight at admission or known history of obesity were not available, therefore we could not explore the association between this variable and the outcomes. We also did not have access to patients' glycaemic control prior to admission, which would have been interesting to analyse. Fourthly, given the retrospective nature of the study, we could not assess if active management of hyperglycaemia could ameliorate the outcomes. To address these limitations additional studies on the impact of glycaemic control in COVID-19 patients are needed.

To our knowledge, this is the first study in Portugal to assess the outcomes of hospitalized COVID-19 patients with diabetes and their association to glucose control status.

Conclusion

In conclusion, T2DM itself was not associated with an increased risk of poor outcomes in our study. However, we present evidence that tight glycaemic control has a protective effect on outcomes of diabetic patients with COVID-19. Gathering several risk factors in COVID-19 patients, such as presence of comorbidities, older age and hyperglycaemia unravels a striking high risk of mortality. In light of the potentially devastating effects of diabetes mellitus, in particular in older patients or those with pre-existing comorbidities, a comprehensive and aggressive monitoring of glucose control is required. Clinicians should maximize TIR in these patients, using a basal-bolus or continuous insulin infusion whenever needed.

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CA, BA: study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation.
MM: study conception and design, supervision.
SP and IP: supervision.
All authors reviewed the results and approved the final version of the manuscript.
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