Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

Comparison of Mortality Rate and Severity of Pulmonary Involvement in Coronavirus Disease-2019 Adult Patients With and Without Type 2 Diabetes: A Cohort Study

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Key Messages

- Patients with type 2 diabetes macrovascular complications are at higher risk of mortality due to coronavirus disease-2019.
- Blood glucose control and insulin therapy in type 2 diabetes patients diagnosed with severe and critical forms of coronavirus disease-2019 are major factors during hospitalization.

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ABSTRACT

Objectives: Patients with diabetes are potentially at higher risk of mortality due to coronavirus disease-2019 (COVID-19). In this study, we aimed to compare the outcomes and severity of pulmonary involvement in COVID-19 patients with and without diabetes.
Methods: In this cohort study, we recruited patients with diabetes who were hospitalized due to COVID-19 during the period from February 2020 to May 2020. Hospitalized individuals without diabetes were enrolled as control subjects. All patients were followed for 90 days and clinical findings and patients' outcomes were reported.
Results: Over a period of 4 months, 127 patients with diabetes and 127 individuals without diabetes with a diagnosis of COVID-19 were recruited. Their mean age was 65.70±12.51 years. Mortality was higher in the group with diabetes (22.8% vs 15.0%; p=0.109), although not significantly. More severe pulmonary involvement (p=0.015), extended hospital stay (p<0.001) and greater need for invasive ventilation (p=0.029) were reported in this population. Stepwise logistic regression revealed that diabetes was not independently associated with mortality (p=0.092). Older age (odds ratio [OR], 1.054; p=0.003), aggravated pulmonary involvement on admission (OR, 1.149; p=0.001), presence of comorbidities (OR, 1.290; p=0.020) and hypothyroidism (OR, 6.576; p=0.021) were associated with mortality. Diabetic foot infection had a strong positive correlation with mortality (OR, 49.819; p=0.016), whereas insulin therapy had a negative correlation (OR, 0.242; p=0.045).
Conclusions: The mortality rate due to COVID-19 did not differ significantly between patients with or without diabetes. Older age, macrovascular complications and presence of comorbidities could increase mortality in people with diabetes. Insulin therapy during hospitalization could attenuate the detrimental effects of hyperglycemia and improve prognosis of patients with COVID-19 and diabetes.

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RÉSUMÉ

Objectifs : Les patients diabétiques sont potentiellement exposés à un risque plus élevé de mortalité liée à la maladie à coronavirus 2019 (COVID-19). Dans la présente étude, nous avions pour objet de comparer les résultats cliniques et la gravité de l'atteinte pulmonaire chez les patients diabétiques ou non diabétiques atteints de la COVID-19.

Méthodes : Dans cette étude de cohorte, nous avons recruté les patients diabétiques qui étaient hospitalisés en raison de la COVID-19 au cours de la période de février 2020 à mai 2020. Les sujets témoins recrutés étaient les individus non diabétiques hospitalisés. Nous avons rapporté les résultats cliniques et l'évolution de l'état de santé de tous les patients suivis durant 90 jours.

Résultats : Au cours de la période de 4 mois, nous avons recruté 127 patients diabétiques et 127 individus non diabétiques qui recevaient un diagnostic de COVID-19. L'âge moyen était de 65,70 ± 12,51 ans. La mortalité était plus élevée dans le groupe des patients diabétiques (22,8 % *vs* 15,0 %; p = 0,109), quoique de façon non significative. Dans cette population, nous avons rapporté l'atteinte pulmonaire plus grave (p = 0,015), le séjour prolongé à l'hôpital (p < 0,001) et la nécessité d'une ventilation effractive (p = 0,029). La régression logistique séquentielle a révélé que le diabète n'était pas indépendamment associé à la mortalité (p = 0,092). Le grand âge (ratio d'incidence approché [RIA], 1,054; p = 0,003), l'atteinte pulmonaire plus grave à l'admission (RIA, 1,149; p = 0,001), la comorbidité (RIA, 1,290; p = 0,020) et l'hypothyroïdisme (RIA, 6,576; p=0,021) étaient associés à la mortalité. Il existait une forte corrélation positive entre l'infection du pied diabétique et la mortalité (RIA, 49,819; p = 0,016), mais une corrélation négative avec l'insulinothérapie (RIA, 0,242; p = 0,045).

Conclusions : Le taux de mortalité lié à la COVID-19 ne diffère pas de façon significative entre les patients diabétiques et les patients non diabétiques. Le grand âge, les complications macrovasculaires et la comorbidité pourraient faire augmenter la mortalité chez les personnes diabétiques. L'insulinothérapie en cours d'hospitalisation pourrait permettre d'atténuer les effets néfastes de l'hyperglycémie et d'améliorer le pronostic des patients diabétiques atteints de la COVID-19.

Introduction

Coronavirus disease-2019 (COVID-19), caused by the novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), can lead to severe pneumonia and multiorgan failure, especially in older patients and those with comorbidities, such as diabetes mellitus (DM), hypertension and cardiovascular disorders (1).

Diabetes has deleterious effects on the immune system and could lead to higher susceptibility to bacterial infections (2,3). In SARS-CoV-1 disease, it has been shown that individuals with pre-existing DM are at increased risk of death (4). Also, in previous retrospective studies, DM has been associated with an increased risk of mortality in SARS-CoV-2 infection (5,6). Until now, cohort studies regarding prognosis of patients with coexistent diabetes and COVID-19 with the same age and sex distribution have not been done.

In this cohort study performed on patients hospitalized for COVID-19, we aimed to determine whether patients with diabetes had worse clinical outcomes and more severe radiologic findings when compared to patients without diabetes.

Methods

Hospital-based cohort study

In this cohort study, 127 patients with diabetes hospitalized for COVID-19 and 127 control subjects without diabetes, also admitted due to COVID-19, were included. All participants were recruited from the Imam Hossein Medical Center, affiliated with the Shahid Beheshti University of Medical Sciences, Tehran, Iran, from February 2020 to May 2020. The ethics committee of the Shahid Beheshti University of Medical Sciences approved the study and all patients signed written informed consent before enrolment. Diagnosis of COVID-19 was confirmed for participants in both the case and control groups by reverse transcript–polymerase chain reaction and/or computed tomography (CT) (7) scan findings. To control blood glucose levels during hospitalization, insulin intensification, basal-bolus insulin regimen, sliding scale or insulin infusion protocols were considered for patients with DM to reach and maintain glucose level between 140 and 180 mg/dL (7.8 to 10.0 mmol/L). Patients were visited daily during hospitalization and followed up for 90 days. All patients received COVID-19 treatment based on the latest interim national guideline for diagnosis and management of COVID-19 (8).

Chest CT interpretation

Patients underwent chest CT examination after admission, and all CT scans were reviewed and reported by the same experienced radiologist. The severity of pulmonary involvement was reported based on a quantitative scoring system (9). A scoring scale from 0 to 5 was considered for each of the lung lobes, based on visual inspection (0 for no involvement in a particular lobe, and 5 for >75% involvement); a score of 1 was considered for <5%, 2 for 5% to 25%, 3 for 26% to 49% and 4 for 50% to 75% of each lobe being involved. The maximum score of 25 was considered when there was involvement of >75% of all 5 lobes of the lung. The predominant patterns on chest CT imaging were classified into 3 groups: ground-glass opacity (GGO), consolidation and GGO/consolidation (mixed). Secondary CT findings, such as pleural effusion, pericardial effusion, cardiomegaly and lymphadenopathy (10) >10 mm, were also recorded. Distribution of lung lesions was grouped into subpleural, peribronchovascular and perihilar categories.

Table 1
Patients' demographics and baseline clinical and laboratory findings

Characteristics	Total (n=254)	Cases (n=127)	Controls (n=127)	p Value
Age, years	65.70±12.51	66.38±12.51	65.03±12.53	0.332
Sex				
Male	142 (55.9)	71 (55.9)	71 (55.9)	1.000
Female	112 (44.1)	56 (44.1)	56 (44.1)	
Positive COVID-19 RT-PCR	194 (76.4)	103 (81.1)	91 (71.7)	0.191
Body mass index, kg/m^2	26.12 (5.16)	26.67 (5.83)	25.71 (4.12)	0.001
Systolic blood pressure, mmHg	119.84±16.69	120.86±18.37	118.84±14.87	0.411
Diastolic blood pressure, mmHg	77.00±9.51	77.64±9.69	76.36±9.80	0.443
CT scan severity index	10.00 (7.00)	11.00 (6.00)	10.00 (6.00)	0.015
Pulse rate, beats/min	88.40±14.99	88.37±15.44	88.42±14.59	0.850
Respiratory rate, breaths/min	18.00 (4.00)	18.00 (2.00)	18.00 (4.00)	0.017
Oxygen saturation	91.00 (6.00)	90.00 (8.00)	93.00 (5.00)	<0.001
ARDS at baseline	27 (10.6)	14 (11.0)	13 (10.0)	0.841
Laboratory data				
Serum creatinine, mg/dL	1.20 (0.60) [0.50–25.00]	1.30 (0.80) [0.70–25.00]	1.20 (0.5) [0.50–8.10]	0.078
Estimated glomerular filtration rate				0.161
>90 mL/min	17 (7.42)	5 (4.50)	12 (9.40)	
60–90 mL/min	76 (33.19)	35 (31.50)	41 (32.30)	
30–60 mL/min	98 (42.80)	48 (43.30)	50 (39.40)	
<30 mL/min	38 (16.59)	23 (20.7)	15 (11.80)	
C-reactive protein, mg/dL	53.00 (45.25) [16.00–72.10]	64.50 (61.88) [2.80–287.00]	54.60 (65.10) [6.00–239.00]	0.664
Erythrocyte sedimentation rate, seconds	47.91±26.10	47.92±27.72	47.90±24.51	0.900
Lactate dehydrogenase, units/L	483.00 (552.00) [374.00–981.00]	334.50 (259.00) [84.00–9,359.00]	427.00 (382.00) [170.00–1,746.00]	0.168
Aspartate aminotransferase, units/L	46.00 (24.00) [23.00-51.00]	31.500 (16.00) [11.00-2127]	33.00 (26.50) [10.00–1,786.00]	0.829
Alanine aminotransferase, units/L	23.00 (18.00) [17.00–38.00]	27.00 (11.00) [13.00–1,314.00]	25.00 (25.00) [10.00–912.00]	0.386
Procalcitonin, ng/mL	0.23 (0.37) [0.07–0.49]	0.30 (0.36) [0.07–8.94]	0.28 (1.11) [0.01–26.94]	0.854
White blood cells, cells/μL	6,100.00 (3,250.00) [4,000.00–9,400.00]	6,800.00 (4,550.00) [2,900.00–26,400.00]	6,400.00 (7,550.00) [2,600.00–27,400.00]	0.066
Neutrophils, %	72.42±12.04	73.44±12.19	71.42±11.85	0.287
Lymphocyte, %	20.27±12.03	19.93±11.39	20.61±10.54	0.554
Hemoglobin, g/dL	12.50±2.00	12.32±2.01	12.68±1.98	0.052
Platelet count ×10^6, cells/μL	199.98±86.26	208.08±91.67	191.40±79.62	0.131
D-dimer, units/mL	564.00 (191.00) [338.00–640.00]	513.50 (1,673.00) [76.00–7,500.00]	576.00 (1,565.00) [140.00–3,888.00]	0.851
Albumin, g/dL	3.80±0.56	3.76±0.51	3.85±0.61	0.052
Creatinine phosphokinase, units/L	123.00 (156.00) [18.00–2,294.00]	146.50 (197.00) [35.00–1,387.00]	113.50 (126.00) [18.00–2,294.00]	0.050
25-dihydroxyvitamin D_3, ng/mL	22.75±12.94	24.18±14.33	20.88±10.74	0.393
Smoking history				0.554
Nonsmoker	240 (94.5)	119 (93.7)	121 (95.3)	
Ex-smoker	5 (2.0)	2 (1.6)	3 (2.4)	
Currently smoking	9 (3.5)	6 (4.7)	3 (2.4)	
Past medical history				
Coexisting disorder				<0.001
Positive	184 (72.4)	118 (92.9)	66 (52.0)	
Negative	70 (27.6)	9 (7.1)	61 (48.0)	
Chronic obstructive pulmonary disease	7 (2.8)	4 (3.1)	3 (2.4)	0.702
Hypertension	109 (42.9)	68 (53.5)	41 (32.3)	0.001
Cerebrovascular accident	21 (8.3)	16 (12.6)	5 (3.9)	0.012
Malignancy	11 (4.3)	4 (3.1)	7 (5.5)	0.355
Immunodeficiency	5 (2.0)	4 (3.1)	1 (0.8)	0.175
Chronic kidney disease	21 (8.3)	16 (12.6)	5 (3.9)	0.012
End-stage renal disease/dialysis	14 (5.5)	9 (7.1)	5 (3.9)	0.271
Ischemic heart disease	64 (25.2)	39 (30.7)	25 (19.7)	0.043
Hypothyroidism	12 (4.7)	6 (4.7)	6 (4.7)	1.000
Diabetic foot infection	6 (2.4)	6 (4.7)	0 (0)	0.013
On admission signs and symptoms				
Cough	163 (64.6)	89 (70.1)	74 (58.3)	0.066
Cough type				0.341
Nonproductive	129 (79.8)	73 (82.0)	56 (75.7)	
Productive	34 (20.2)	16 (18.0)	18 (24.3)	
Fatigue	92 (36.2)	49 (38.6)	43 (33.9)	0.433
Nausea/vomiting	44 (17.3)	26 (20.5)	18 (14.2)	0.185
Abdominal pain	16 (6.3)	7 (5.5)	9 (7.1)	0.605
Diarrhea	16 (6.3)	11 (8.7)	5 (3.9)	0.121
Chills	62 (24.4)	33 (26.0)	29 (22.8)	0.559
Fever	109 (42.9)	53 (41.7)	56 (44.1)	0.704
Anorexia	43 (16.9)	21 (16.5)	22 (17.3)	0.867
Headache	20 (7.9)	10 (7.9)	10 (7.9)	1.000
Loss of consciousness	16 (6.3)	11 (8.7)	5 (3.9)	0.121
Seizure	5 (2.0)	4 (3.1)	1 (0.8)	0.175
Myalgia	74 (29.1)	36 (28.3)	38 (29.9)	0.782
Chest pain	29 (11.4)	14 (11.0)	15 (11.8)	0.861
Dyspnea	152 (59.8)	83 (65.4)	69 (54.3)	0.073

ARDS, acute respiratory distress syndrome; *COVID-2019*, coronavirus disease-2019; *CT*, computed tomography; *RT-PCR*, reverse transcript–polymerase chain reaction.
Note: Data expressed as mean ± standard deviation, number (%) or number (%) [range].

Data collection

The attending physician collected demographic data for all recruited patients. Primary clinical and laboratory data, including glycemic control profile, inflammatory marker panel, complete blood count with differentiation, renal and hepatic function profiles, electrolytes, blood pressure, ventilation and oxygen saturation status, were documented. All patients were assessed with regard to comorbidities, underlying diseases and drug history. The data for type of hypoglycemic agents (i.e. insulin therapy or oral hypoglycemic agents) given to patients with diabetes were also compiled.

Primary outcome

Mortality rate was assessed during hospitalization and for up to 90 days after disease onset.

Secondary outcomes

Oxygen requirement, mechanical ventilation, duration of hospital stay, acute respiratory distress syndrome (11) occurrence (11,12), shock and multiorgan failure were all considered as secondary outcomes (13). The Charlson index was utilized to assess the prognostic effects of comorbidities (14).

Statistical analysis

Analysis was performed using STATA version 14 (StataCorp, College Station, Texas, United States) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Data were assessed for parametric and nonparametric distribution by the Kolmogorov-Smirnov test. Quantitative variables with a normal distribution are reported as mean ± standard deviation and those with a non-normal distribution are reported as median (interquartile range). Qualitative variables are presented as frequency and percent. Categorical data were analyzed by chi-square test or Fisher's exact test (if >25% of the categories had frequencies <5). Differences in continuous data were compared using a t test or a Mann-Whitney *U* test in the bivariant situation. $p<0.05$ was considered significant. We used multivariable logistic regression to evaluate the association between covariates and outcomes among the patients studied. Glycated hemoglobin (A1C) stepwise selection methods were used (backward and forward) to select a set of candidate predictors for inclusion in the multivariate model. The overall performance of models was evaluated using the Brier score, Nagelkerke's R^2 and area under the curve were calculated for discrimination, and the Hosmer-Lemeshow test was used for evaluation of calibration. Odds ratios and 95% confidence intervals were calculated. $p<0.05$ was considered significant for uni- and multivariate regression analyses.

The study was approved by the ethics committee Shahid Beheshti University of Medical Sciences (Code No. IR.SBMU.RETECH.REC.1399.063).

Results

By the end of the study period, 127 patients with diabetes (case group) and 127 patients without diabetes (control group) had been enrolled and followed up for 90 days. Participants were 65.70±12.51 years of age (mean ± standard deviation). Baseline demographics on admission to the laboratory and physical findings are presented in Table 1. All patients in the case group had type 2 diabetes. Ten patients were diagnosed with type 2 diabetes during hospitalization for COVID-19. Twenty-three patients had a history of type 2 diabetes of ≤5 years. Thirty-eight, 24 and 32 patients had a history of type 2 diabetes for 5 to 10 years, 10 to 15 years and >15 years, respectively. No correlation was found between the duration of diabetes and mortality (p=0.317). Mean A1C level for patients with diabetes was 9.15±2.21%. According to the latest guidelines for glycemic control from the American Diabetes Association and Diabetes Canada (15,16), 97 patients (76%) had uncontrolled DM at the time of admission based on their initial A1C level of >7%. DM was treated with insulin in 39 patients. In 78 and 10 patients, oral hypoglycemic agents and nutritional diet intervention, respectively, were utilized. During hospitalization, a basal-bolus regimen, sliding scale and insulin infusion were considered for 55, 10 and 4 patients, respectively, with poorly controlled diabetes. Furthermore, 28 patients received insulin intensification for uncontrolled blood glucose. Eventually, blood glucose levels in 78% of patients with diabetes were controlled during hospitalization. Six patients had at least 1 episode of hypoglycemia (defined as blood glucose levels <70 mg/dL [<3.9 mmol/L]) (17,18).

No significant differences were observed for frequency of steroid utilization in the 2 groups (p=0.197); steroids were used in 7 (5%) and 3 (2%) individuals in the case and control groups, respectively. Four patients in the case group were hospitalized due to recent cerebrovascular accident, after which they were diagnosed with COVID-19.

Significantly higher respiratory rate (p=0.017) and lower oxygen saturation (p<0.001) were recorded in patients with diabetes on admission; these patients also had more severe pulmonary involvement and higher CT scan severity indices (p=0.0015). At baseline, there was no significant difference in development of acute respiratory distress syndrome (ARDS) between the 2 groups (p=0.841). As shown in Table 2, GGO was the most common pattern on CT scans of all patients. Compared to patients without diabetes, consolidation was more frequently observed in patients with diabetes (p=0.01). The right and left lower lobes were the lobes with the highest percentage of involvement in all patients (85.4% and 85.8%, respectively). The left upper and lower lobes were more likely to be involved in patients with diabetes compared to their counterparts without diabetes (p=0.07 and p=0.06, respectively). Lung lesions were mostly distributed in the subpleural area (68.1%),

Table 2
Computed tomography findings of patients

Variables	Total (n=254)	Cases (n=127)	Controls (n=127)	p Value
Pattern of involvement				
GGO	139	68	71	0.53
Consolidation	62	40	22	0.01
GGO/consolidation	28	14	14	0.93
Distribution of lesions				
Subpleural	173	79	94	0.01
Perihilar	2	0	2	0.24
Peribronchovascular	98	50	48	0.96
Other findings				
Cardiomegaly	3	1	2	0.62
Lymphadenopathy >10 mm	—	—	—	—
Pericardial effusion	3	2	1	1.00
Pleural effusion	21	9	12	0.44
Lung lobe involvement				
Right upper lobe	205 (80.7)	108 (85.0)	97 (76.4)	0.17
Right middle lobe	195 (76.8)	104 (81.9)	91 (71.7)	0.11
Right lower lobe	217 (85.4)	114 (89.8)	103 (81.1)	0.11
Left upper lobe	209 (82.3)	111 (87.4)	98 (77.2)	0.07
Left lower lobe	218 (85.8)	115 (90.6)	103 (81.1)	0.06

GGO, ground-glass opacity.
Note: Data expressed as number or number (%).

a distribution type that was significantly more common among patients without diabetes (p=0.01).

After the 90-day period of follow up, of 254 subjects, 48 (18.9%) had died during the treatment or follow-up period. Ten patients were rehospitalized after discharge. Mortality was higher amongst the population with DM compared with the control group (22.8% to 15.0%), but the difference was not statistically significant (p=0.109). Furthermore, a statistically significant longer hospital stay was recorded in patients with diabetes (7 vs 5 days, p<0.001). ARDS, septic shock and multiorgan failure were observed in 40, 21 and 25 patients, respectively, during hospitalization. No statistically significant differences were observed between the 2 groups of patients with regard to secondary outcomes (Table 3).

Logistic regression was performed in both the total population (254 patients) and in the patients with diabetes (n=127). Discrimination indexes, R^2=0.433, Brier = 0.102 for total population and R^2=0.443, Brier=0.113 in the population with diabetes were calculated. Area under the curve was 0.874 and 0.844 for the model for the total population and DM population, respectively. The goodness-of-fit test (Hosmer-Lemeshow) resulted in p=0.293 and p=0.179 for the logistic regression model in the total population and DM population, respectively. In the multivariate logistic regression analysis for the total population, older age (odds ratio [OR], 1.054 [1.017 to 1.092]; p=0.003), higher CT severity index (OR, 1.149 [1.054 to 1.252]; p=0.001), Charlson index (OR, 1.290 [1.040 to 1.601]; p=0.020) and history of hypothyroidism (OR, 6.576 [1.325 to 32.626]; p=0.021) were associated with mortality. Also, higher oxygen saturation at baseline (OR, 0.939 [0.909 to 0.970]; p<0.001) was shown to be a protective factor. Diabetes was not significantly associated with mortality (p=0.092). Among patients with diabetes, age (OR, 1.065 [1.009 to 1.123]; p=0.023), CT severity index (OR, 1.202 [1.058 to 1.365]; p=0.005), Charlson index (OR, 1.480 [1.106 to 1.981]; p=0.008) and presence of diabetic foot infection (OR, 49.819 [2.0492 to 1211.186]; p=0.016) were associated with higher mortality, but insulin therapy was shown to be a protective factor (OR, 0.242 [0.061 to 0.967]; p=0.045). Higher body mass index (BMI) (p=0.118), A1C level (p=0.585) and controlled vs uncontrolled diabetes based on A1C level (p=0.201) showed no association with mortality in patients with DM.

Discussion

Our cohort study has demonstrated that diabetes per se is not associated with a statistically significant increase in mortality due to COVID-19. However, patients with diabetes had more severe pneumonia and a more severe course of illness; these patients had a lower oxygen saturation and a higher respiratory rate on admission compared with the control group. We observed a significantly greater extent of pulmonary involvement in patients with diabetes by evaluating and scoring the chest CT scans in our population, with the involvement of subpleural area mostly in the lower lobes. This group of patients also had higher rates of intubation, a need for mechanical ventilation support and extended hospitalization.

Our study differs significantly from previous studies, which considered diabetes and uncontrolled blood glucose level as independent risk factors for mortality in COVID-19 (19). In those retrospective studies, patients with diabetes had different age distributions, and the patients were not age- and sex-matched with a control group of patients without diabetes. Also, the sample sizes in the 2 groups were considerably different (5,6,19,20). In 2 large-scale retrospective population-based studies conducted in England, patients with diabetes were shown to be at increased risk for mortality due to COVID-19 (21,22). Subgroup analysis of the A1C levels in those studied demonstrated that patients with type 2 uncontrolled diabetes are at increased risk of death. In our study, we included individuals with or without diabetes in a 1:1 ratio, with no differences in age and sex distributions as remarkable confounding factors in the mortality of patients with COVID-19.

A notable finding in our study is that duration of diabetes and previous long-term hyperglycemia (evaluated by A1C measurement at admission) did not show any association with mortality. Recently, in the CORONADO study, Cariou et al reported that in patients with coexistent COVID-19 and diabetes, A1C level, representative of long-term glucose control, was not associated with tracheal intubation and/or death, a finding similar to that of our study (7). It has previously been reported that there are no significant differences between the severity of pulmonary involvement and mortality in patients with well-controlled and poorly controlled diabetes and COVID-19 based on A1C levels (23). In individuals with diabetes, acute hyperglycemia during the hospital stay due to stressful conditions, such as hypoxia, fever, medication side effects, cytokine storm and disease severity, could cause insulin resistance (24,25). Furthermore, it has been speculated that SARS coronavirus, via binding angiotensin-converting enzyme-2 (ACE-2) to the pancreas, can destroy beta cells and induce acute hyperglycemia (26). All these factors could weaken the value of A1C as a good prognostication index in patients with COVID-19.

Zhu et al demonstrated that, even though type 2 diabetes correlated with a higher mortality rate in patients with COVID-19, well-controlled blood glucose (upper limit <180 mg/dL per 10 mmol/L) during hospitalization was associated with significantly lower mortality compared to individuals with uncontrolled blood glucose (20). In our study, insulin therapy was considered for all patients in the case group with uncontrolled blood glucose levels to achieve a blood glucose level of 140 to 180 mg/dL (7.8 to 10.0 mmol/L), and the statistical analysis showed a significant negative association between insulin therapy and COVID-19 mortality. Initially, it was hypothesized that patients receiving insulin would be at higher risk of COVID-19 mortality due to uncontrolled and more likely longer durations of diabetes. However, in the subgroup analysis, we observed that patients who received insulin therapy had a decreased mortality risk of about 75%, a finding that could be attributed to optimal blood glucose control during hospitalization and is in line with a previously cited study (20). We do not have data on treatment strategies from studies concluding that patients with uncontrolled diabetes based on A1C levels have higher mortality rates compared to those with controlled diabetes (21,22). It is expected that patients with uncontrolled diabetes would have more frequent episodes of hyperglycemia during their hospital stay, but it is not clear what glucose control strategies were implemented and how effectively these strategies were carried out. In a retrospective study conducted in the United States in 88 hospitals, among 1,122 patients, individuals with uncontrolled hyperglycemia (defined as ≥2 blood glucose test levels at >180 mg/dL

Table 3
Length of hospital stay and outcome

Variables	Total (n=254)	Cases (n=127)	Controls (n=127)	p Value
Ventilation type, n (%)				0.029
Invasive	27 (10.6)	19 (15.0)	8 (6.3)	
Noninvasive	227 (89.4)	108 (85.0)	119 (93.7)	
Secondary outcomes, %				
ARDS	40	21	19	0.432
Septic shock	21	13	8	0.181
Multiorgan failure	25	15	10	0.200
Hospital length of stay (days) [range]	6 (7) [1–60]	7 (7) [1–60]	5 (7) [1–34]	<0.001
Outcome, n (%)				0.109
Death	48 (18.9)	29 (22.8)	19 (15.0)	
Recovery	206 (81.1)	98 (77.2)	108 (85.0)	

ARDS, acute respiratory distress syndrome.

within a 24-hour period during hospitalization) were shown to have noticeably higher mortality rates (27).

In our experience, insulin therapy and good control of blood glucose levels could ameliorate the negative effects of hyperglycemia on patient outcomes.

Another factor could be the effects of insulin on the immune system with some immunomodulatory characteristics (28). Given the hyperinflammatory state and cytokine storm occurring during SARS-CoV-2 infection, these characteristics may play a major role, and insulin administration in patients with diabetes and COVID-19 may attenuate the magnitude of the inflammatory response (29).

Obesity is another major factor in the setting of severe infections, due to an impaired immune system, and could also reveal a restrictive pattern in pulmonary function studies (30,31). The CORONADO study showed that BMI was associated with tracheal intubation rate rather than mortality; however, the association was less prominent in patients with morbid obesity (7). Simmonet et al revealed an association between obesity and mechanical ventilation requirement (32), yet our study did not show a significant association between BMI and mortality. It needs to be mentioned that, in our study, the median BMI in the case group was 26.7 kg/m^2 compared with 28.4 kg/m^2 in the CORONADO study and 29.6 kg/m^2 in the study by Simonnet et al (7,32). The difference between the findings of our study and the other 2 studies could be due to ethnical and geographic variations.

Ischemic heart disease, chronic kidney disease, diabetic foot infection and cerebrovascular accident were more prevalent in our patients with diabetes. An unexpected vascular event, such as ischemic stroke, occurred in 4 patients in the DM population, but none in the control group. Controlled diabetes without vascular complications or even short-term, uncomplicated, uncontrolled diabetes were not found to be associated with increased mortality due to COVID-19. Patients with confirmed microvascular complications, such as diabetic foot infection, which occur in patients with long-lasting uncontrolled diabetes (33), are at significantly higher risk of death (7,34). In our subgroup analysis, in individuals with diabetes, there was a significant association between diabetic foot infection and mortality, with a 50-fold increase in the rate of mortality. Low-grade inflammation induced by DM causes damage to the vascular system, and diabetes is a major risk factor for cardiovascular events (35). Death due to cardiovascular events has been shown to be more prevalent in COVID-19 patients (36). However, it is important to consider that DM per se, without vascular complications, may not be associated with increased mortality in COVID-19.

Another major aspect that needs consideration is presence of comorbidities in patients with or without diabetes. Different underlying conditions, such as hypertension, have previously been considered risk factors for severity of COVID-19 (7,37), and, when it coexists with diabetes, more detrimental effects can be expected. In our study, comorbidities were associated with a significant increase in mortality in the total population, and the risk was even higher in patients with DM. We assessed the effect of underlying conditions via the Charlson comorbidity index; a higher Charlson score, that is, a higher number of serious underlying diseases, was associated with an increased risk of mortality.

Interestingly, hypothyroidism was shown to be an independent risk factor of mortality in the total population and could increase mortality by 7-fold in COVID-19 patients without hypothyroidism. It has been demonstrated that hypothyroidism could be related to the decrease in the ACE serum level, and, in turn, this could lead to an increase in ACE receptor expression, which plays a fundamental role in the SARS-CoV-2 cell entry mechanism (38–40). Thyroid dysfunction could be more prevalent in critically ill patients (41), which may increase mortality in these patients (42,43). Given the critical condition of many COVID-19 patients and the potential effects of hypothyroidism on mortality, it seems reasonable to assess thyroid function in all COVID-19 patients.

Our investigation was done at a single centre, and it lacked racial diversity, which is a study limitation even though the hospital was a referral centre for COVID-19.

Diabetes per se was not associated with significantly higher mortality due to COVID-19. Regardless of baseline A1C levels, insulin therapy and tight control of blood glucose levels during hospitalization can improve the prognosis and decrease the mortality rate of individuals with coexistent COVID-19 and type 2 diabetes. These findings suggest that the greater pulmonary involvement seen on CT scans of patients with diabetes does not necessarily indicate higher mortality likelihood, and thus physicians should be aware that appropriate blood glucose management of such patients with insulin therapy may be beneficial. Our findings show that a history of hypothyroidism increases the risk of mortality. More studies with larger sample sizes are needed to assess the effects of metabolic and endocrine conditions on patients with COVID-19.

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Conflicts of interest: None.

Author Contributions

S.K. conceptualized the study and researched the data, O.M. wrote the manuscript, M.S. reviewed/edited the manuscript, R.M. researched the data, A.K. researched the data and reviewed the manuscript and M.S. researched the data and reviewed/edited the manuscript.

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