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Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Association of diabetes mellitus with disease severity and prognosis in COVID-19: A retrospective cohort study

Yan Zhang [a,1], *Yanhui Cui* [a,1], *Minxue Shen* [b,c,1], *Jianchu Zhang* [d], *Ben Liu* [e], *Minhui Dai* [a], *Lingli Chen* [a], *Duoduo Han* [a], *Yifei Fan* [a], *Yanjun Zeng* [a], *Wen Li* [a], *Fengyu Lin* [a], *Sha Li* [f], *Xiang Chen* [b,*], *Pinhua Pan* [a,*],

The medical team from Xiangya Hospital to support Hubei, China

[a] *Department of Respiratory Medicine, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China*
[b] *Department of Dermatology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China*
[c] *Department of Social Medicine and Health Management, Xiangya School of Public Health, Central South University, Changsha, Hunan 410008, China*
[d] *Department of Respiratory Medicine, Union Hospital of Huazhong University of Science and Technology, Wuhan, Hubei 430022, China*
[e] *Department of Emergency, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China*
[f] *Department of Radiology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China*

ARTICLE INFO

Article history:
Received 29 March 2020
Received in revised form
7 May 2020
Accepted 16 May 2020
Available online 22 May 2020

Keywords:
Diabetes mellitus
COVID-19
SARS-CoV-2
Prognosis

ABSTRACT

Aims: The 2019 novel coronavirus disease (COVID-19) emerged in Wuhan, China, and was characterized as a pandemic by the World Health Organization. Diabetes is an established risk associated with poor clinical outcomes, but the association of diabetes with COVID-19 has not been reported yet.

Methods: In this cohort study, we retrospectively reviewed 258 consecutive hospitalized COVID-19 patients with or without diabetes at the West Court of Union Hospital in Wuhan, China, recruited from January 29 to February 12, 2020. The clinical features, treatment strategies and prognosis data were collected and analyzed. Prognosis was followed up until March 12, 2020.

Results: Of the 258 hospitalized patients (63 with diabetes) with COVID-19, the median age was 64 years (range 23–91), and 138 (53.5%) were male. Common symptoms included fever (82.2%), dry cough (67.1%), polypnea (48.1%), and fatigue (38%). Patients with diabetes had significantly higher leucocyte and neutrophil counts, and higher levels of fasting blood glucose, serum creatinine, urea nitrogen and creatine kinase isoenzyme MB at admission compared with those without diabetes. COVID-19 patients with diabetes were more likely to develop severe or critical disease conditions with more complications, and had higher incidence rates of antibiotic therapy, non-invasive and invasive mechanical ventilation, and death (11.1% vs. 4.1%). Cox proportional hazard model showed that diabetes (adjusted hazard ratio [aHR] = 3.64; 95% confidence interval [CI]: 1.09, 12.21) and fasting blood glucose

* Corresponding authors.
E-mail addresses: chenxiangck@126.com (X. Chen), pinhuapan668@csu.edu.cn (P. Pan).
[1] These authors contributed equally to the study.
https://doi.org/10.1016/j.diabres.2020.108227

(aHR = 1.19; 95% CI: 1.08, 1.31) were associated with the fatality due to COVID-19, adjusting for potential confounders.

Conclusions: Diabetes mellitus is associated with increased disease severity and a higher risk of mortality in patients with COVID-19.

1. Introduction

Since December 2019, China has been experiencing an outbreak of pneumonia with a novel coronavirus [1], which was officially named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV). The World Health Organization (WHO) has declared that Coronavirus Disease 2019 (COVID-19) is caused by SARS-CoV-2 infection. WHO characterized COVID-19 as a pandemic, as it has spread rapidly throughout China and more than 100 countries in the following months after the outbreak, causing more than 150,000 confirmed cases and thousands of deaths by March 15, 2020. SARS-CoV-2 belongs to the subgenus Sarbecovirus (β-CoV lineage B), and shares 79% of sequence with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), but only 50% homology with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [2,3].

China has had a climbing prevalence rate of diabetes in recent decades. According to the latest nationally representative cross-sectional survey among 170,287 participants in 2013 in mainland China, the overall prevalence of diabetes was 10.9% in adults and 20.2% in the elderly [4]. Patients with diabetes are more susceptible to be infected by bacteria, viruses, and fungus than individuals without diabetes owing to relatively lower immune function [5,6]. As a result, these patients might be at an increased risk of SARS-CoV-2 infection and consequently poor prognosis.

Although many studies have described the clinical characteristics of COVID-19, so far [1,7-9], information with respect to diabetes among these patients, has not been well characterized yet. In the current study, we retrospectively reviewed the clinical data of 258 patients with laboratory-confirmed COVID-19, and compared the differences in clinical characteristics, laboratory markers, treatment strategies, and short-term prognosis including death between patients with and without diabetes. We hope that these findings will provide new insights into the risk stratification, disease management, and therapeutic strategies for COVID-19 patients with diabetes.

2. Methods

2.1. Study design and participants

This was a retrospective cohort study among patients with COVID-19. All patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to several isolation wards at the West Court of Union Hospital of Huazhong University of Science and Technology from January 29 to February 12, 2020, were enrolled in the study. West Court of Union Hospital, located in Wuhan, Hubei Province, the epidemic areas of COVID-19, is one of the major tertiary teaching hospitals, and has been mainly responsible for the treatments of COVID-19 patients assigned by the government. Professor Pinhua Pan, from Department of Respiratory Medicine in Xiangya Hospital, Central South University, was assigned as the director of National Medical Team of aiding Hubei from Xiangya Hospital to guide the clinical work for the treatment of COVID-19 in Union Hospital of Huazhong University of Science and Technology, Wuhan. All patients with COVID-19 enrolled in this study were diagnosed according to World Health Organization interim guidance [10]. This study was approved by the institutional ethics board of Union Hospital of Huazhong University of Science and Technology and ethics board of Xiangya Hospital, Central South University (No.202003049). Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

2.2. Measurements

Demographic, clinical features, laboratory and radiological findings, treatment strategy, and short-term prognosis data of the patients were obtained from their medical records. Clinical outcomes were followed up to March 12, 2020. All the data was checked by two senior physicians (P.P and J.Z). All the patients enrolled in this study were laboratory-confirmed COVID-19 patients, and the diagnostic criteria of COVID-19 was based on the positive detection of viral nucleic acids. The severity of COVID-19 was defined based on the diagnostic and treatment guidelines (Version 5–7) by the National Health Committee of China. Severe subtype was defined if a patient met one of the following criteria: (1) Respiratory distress with respiratory frequency $\geq$ 30/min; (2) Pulse oximeter oxygen saturation $\leq$ 93% at rest; (3) Oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2) $\leq$ 300 mmHg. Critically ill subtype followed the criteria mentioned above, and met one of the following criteria: (1) Needs mechanical ventilation due to respiratory failure; (2) shock; (3) combined with multiple organ failure requiring transfer to intensive care unit (ICU).

Pharyngeal swab specimens were collected from each patient for viral nucleic acid detection of SARS-CoV-2 using a real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay as previously described [11]. The viral nucleic acid testing was carried out by the clinical laboratory of Union Hospital of Huazhong University of Science and Technology in Wuhan. Laboratory indicators on admission, including the numbers of leucocytes, neutrophils, lymphocytes, per-

centages of lymphocyte, eosinophils, concentrations of C-reactive protein (CRP), procalcitonin (PCT), fasting blood glucose (FBG), lactate dehydrogenase (LDH), serum creatine kinase (CREA), blood urea nitrogen (BUN), creatine kinase isoenzyme MB (CK-MB), D-dimer, international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) were determined for each patient. All medical laboratory data was generated by the clinical laboratory of Union Hospital of Huazhong University of Science and Technology.

All data was reviewed and transferred to the standardized forms from the electronic medical records in the hospital, including case report forms, nursing records, laboratory and radiological findings. Two senior physicians (P.P and J.Z) independently reviewed the data. Information on demographic data, symptoms, preexisting chronic comorbidities, computed tomographic images of chest, laboratory results were collected. All treatment strategies were recorded during the hospitalization, such as antiviral therapy, antibiotic therapy, use of corticosteroid, and respiratory support. The time from the onset of the illness to the hospital admission was also recorded.

2.3. Definition of conditions

Patients with diabetes were identified based on the patient's documented medical history and guidelines for the prevention and control of T2D in China [12]. Cardiovascular disease including coronary artery disease, congestive heart failure, or a history of myocardial infarction were included; reports of isolated hypertension were not included. Chronic pulmonary disease, chronic obstructive pulmonary disease (COPD), allergic airway disease or the use of supplemental oxygen at home was included. The presence of ARDS was designated by The berlin definition [13]. Cardiac injury was identified when the serum level of hypersensitive cardiac troponin I (hsTNI) was above the upper limit of the normal range or new abnormalities were shown in electrocardiography and echocardiography [14]. Acute kidney injury (AKI) was classified on the basis of the highest serum creatinine level or urine output criteria based on KDIGO clinical practice guideline for AKI [15]. Prognosis was defined based on the patient being discharged from hospital, not discharged yet, or death during hospitalization. The follow-up observation was conducted before March 12, 2020.

2.4. Statistical analysis

Continuous variables were shown as median and interquartile range (IQR), and compared by the Mann-Whitney test since most laboratory data was with skewed distribution. Categorical variables were presented as counts and proportions, and compared by Chi-square test or Fisher's exact test. The Cox proportional hazard model was used to determine the associations of diabetes and FBG with fatality of COVID-19, and adjusted for potential confounders. Adjusted hazard ratio (aHR) with 95% confidence interval (CI) was presented as the effect size. All statistical analyses and graphs were generated and plotted using the GraphPad Prism version 7.00 software (GraphPad Software Inc) or SPSS version 25.0 (IBM, United States). A P value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the patients of COVID-19

A total of 258 consecutive laboratory-confirmed patients with SARS-CoV-2 infection were included and analyzed in the study, and 24% of them had diabetes. Demographic and clinical characteristics of the patients on admission were summarized by diabetes in Table 1. The median age was 64 years (IQR, 56–70; range, 23–92 years), and 138 (53.5%) were male. The median duration from the onset of illness to hospital admission was 12 days (IQR, 7–15). The most common symptoms at the onset of illness were fever (212 [82.2%]), dry cough (173[67.1%]), polypnea (124 [48.1%]), and fatigue (98 [38%]). One hundred seventy-four patients (67.4%) had other preexisting chronic comorbidities, including hypertension (38.0%), cardiovascular disease (15.1%), cerebrovascular disease (4.7%), chronic pulmonary disease (3.5%), chronic kidney disease (3.5%), chronic liver disease (1.2%), and cancer (4.7%). There were no significant differences between patients with and without diabetes, with respect to age, sex, days of illness before hospital admission, and clinical signs and symptoms. Compared with those without diabetes, patients with diabetes were more likely to have comorbidities of cardiovascular disease (23.8% vs. 12.3%, $P = 0.027$) and chronic kidney disease (8.8% vs. 2.1%, $P = 0.027$).

3.2. Laboratory and radiological findings in patients of COVID-19 on admission

The laboratory and radiological findings on admission of the COVID-19 patients with or without diabetes were presented in Table 2. The blood cell tests showed that most patients (81.0%) had normal leukocyte count at the time of hospital admission, while 10.1% had increased leucocyte count and 8.9% had low leucocyte count. However, the COVID-19 patients with diabetes had a higher median leucocyte count (median: 6.34[IQR: 4.66, 8.15] $\times$ 10^9/L vs. median: 5.45[IQR: 4.31, 7.19] $\times$ 10^9/L, $P = 0.039$) and median neutrophils count (median: 4.49[IQR: 3.12, 6.91] $\times$ 10^9/Lvs. median: 3.82[IQR: 2.81, 5.39] $\times$ 10^9/L, $P = 0.022$) compared with those of patients without diabetes. COVID-19 patients with diabetes had more leucocyte increase (20.6% vs. 6.7%) but less leucocyte decrease (4.8% vs. 10.3%, $P = 0.004$) than those patients without DM. The neutrophil-to-lymphocytes ratio (NLR) was significantly higher in patients with diabetes compared to those without diabetes (median: 4.56[IQR: 2.69, 9.51] vs. median: 3.8[IQR: 2.25, 6.31], $P = 0.043$). Interestingly, decreased eosinophil count was also common in these patients (43%), but no significant difference in eosinophil count and the ratio of patients with decreased eosinophil count was found in patients with or without DM. Besides, a positive correlation between eosinophil and lymphocytes numbers on admission was observed (Data not shown), which was consistent with previous study [16]. Other laboratory findings showed no significant differences between the two groups of patients with respect to serum levels of CRP, PCT, and LDH, but COVID-19 patients

Table 1 – Characteristics of the patients with COVID-19.

Characteristics	Total (N = 258)	DM (n = 63)	Non-DM (n = 195)	P
Age (year), median (IQR)	64 (56, 70)	65 (57–71)	64 (55–70)	0.092
Sex, n (%)				0.211
Men	138 (53.5)	38 (60.3)	100 (51.3)	
Women	120 (46.5)	25 (39.7)	95 (48.7)	
Onset of symptoms to hospital admission	12 (7, 15)	11 (8, 15)	12 (7, 15)	0.748
Symptoms, n (%)				
Fever	212 (82.2)	50 (79.4)	162 (83.1)	0.503
Dry cough	173(67.1)	45 (71.4)	128 (65.6)	0.396
Polypnea	124 (48.1)	31 (49.2)	93 (47.7)	0.834
Fatigue	98 (38.0)	22 (34.9)	76 (29.5)	0.738
Expectoration	70 (27.1)	21 (33.3)	49 (25.1)	0.203
Diarrhea	55 (21.3)	17 (27.0)	38 (19.5)	0.207
Myalgia	40 (15.5)	12 (19.0)	28 (14.4)	0.371
Nausea	31 (12.0)	5 (7.9)	26 (13.3)	0.252
Headache	28 (10.9)	3 (4.8)	25 (12.8)	0.074
Vomiting	22 (8.5)	6 (9.5)	16 (6.2)	0.745
Chest pain	14 (5.4)	2 (3.2)	12 (4.7)	0.364
Pharyngalgia	8 (3.1)	4 (6.3)	4 (2.1)	0.087
Preexisting condition, n (%)				
Hypertension	98 (38.0)	29 (46)	69 (35.4)	0.130
Cardiovascular disease	39 (15.1)	15 (23.8)	24 (12.3)	0.027
Cerebrovascular disease	12 (4.7)	3 (4.8)	9 (4.6)	0.962
Chronic pulmonary disease	9 (3.5)	2 (3.2)	7 (3.6)	0.876
Chronic kidney disease	9 (3.5)	5 (8.8)	4 (2.1)	0.027
Chronic liver disease	3 (1.2)	2 (3.2)	1 (0.5)	0.087
Cancer	12 (4.7)	2 (3.2)	10 (5.1)	0.522

DM, diabetes mellitus; IQR, interquartile range.

with diabetes had higher levels of FBG (median: 7.54[IQR: 6.37, 10.62] mmol/L vs. median: 5.81[IQR: 5.32, 6.59] mmol/L, $P < 0.001$), CREA (median: 74[IQR: 64.25, 95.78] μmol/L vs. median: 67.8[IQR: 57.2, 78.23] μmol/L, $P = 0.005$), BUN (median: 5.9 [IQR: 4.09, 8.62] mmol/L vs. median: 4.41[IQR: 3.58, 5.57] mmol/L, $P < 0.001$), and CK-MB (median: 14[IQR: 10, 17] U/L vs. median: 11[IQR: 9, 14] U/L, $P = 0.042$) than those patients without diabetes. For coagulation function markers, patients with diabetes showed a slightly longer of TT (median: 16.1 [15.25, 16.65] sec vs. median: 15.5[IQR: 14.9, 16.23] sec, $P = 0.035$) than those patients without diabetes. The radiological CT images showed that the majority of patients (99.6%) had abnormal results with bilateral lesions.

3.3. *Analysis of severity, treatment and prognosis of patients with COVID-19*

Next, we compared the severity, treatment, and short-term prognosis of the COVID-19 patients with and without diabetes in Table 3. Compared with non-diabetes subjects, patients with diabetes were more likely to develop severely or critically ill subtypes ($P = 0.028$) with more complications including acute respiratory distress (38.1% vs. 19.5%, $P = 0.001$), acute cardiac injury (14.5% vs. 5.1%, $P = 0.016$), and had more antibiotic therapy (74.6% vs. 59.0%, $P = 0.026$), non-invasive and invasive mechanical ventilation ($P = 0.037$). As of March 12, 2020, only 33.7% patients were discharged from the hospital. Patients with diabetes had a higher fatality rate than those without diabetes (11.1% vs. 4.1%, $P = 0.039$).

3.4. *Analysis of associations of diabetes and FBG with death in COVID-19 patients*

To further assess the association of diabetes and FBG with the fatality of COVID-19, Cox proportional hazard model was carried out, and the results (Table 4) showed that comorbid diabetes was an independent risk factor for death in COVID-19 patients, after adjusting for age (aHR = 2.804; 95% CI: 1.01, 7.80; $P = 0.048$) and additionally adjusting for the cardiovascular diseases and chronic kidney diseases (aHR = 2.84; 95% CI: 1.01, 8.01; $P = 0.048$) or additionally adjusting for laboratory markers (aHR = 3.64; 95% CI: 1.09, 12.21; $P = 0.036$). We also found that a higher FBG level on admission was an independent predictor for death in COVID-19 patients as well, after adjusting for the aforementioned covariates (aHR = 1.19, 95% CI: 1.08, 1.31; $P < 0.001$).

4. Discussion

In this retrospective cohort study, we characterized 258 COVID-19 patients with respect to demographics, clinical features, preexisting chronic comorbidities, treatment, and short-term prognosis. We found that COVID-19 patients had a relatively high proportion (24%) of diabetes, and demonstrated that diabetes was associated with alterations in laboratory markers, more severe clinical subtypes at the time of presentation, and worse prognosis compared to those without diabetes, after SARS-CoV-2 infection.

Table 2 – Laboratory and radiological findings of COVID-19 patients at admission.

Variable	Total (N = 258)	DM (n = 63)	Non-DM (n = 195)	P
WBC ($\times10^9$/L), median (IQR)	5.64 (4.37, 7.39)	6.34 (4.66, 8.15)	5.45 (4.31,7.19)	0.039
>9.5 $\times$ 10^9/L, n (%)	26 (10.1)	13 (20.6)	13 (6.7)	0.004
3.5–9.5 $\times$ 10^9/L, n (%)	209 (81.0)	47 (74.6)	162 (83.1)	
<3.5$\times$ 10^9/L, n (%)	23 (8.9)	3 (4.8)	20 (10.3)	
Neutrophil ($\times10^9$/L), median (IQR)	3.92 (2.85, 5.83)	4.49 (3.12, 6.91)	3.82 (2.81, 5.39)	0.022
Lymphocyte ($\times10^9$/L), median (IQR)	1.01 (0.71, 1.38)	1.1 (0.65, 1.41)	0.995 (0.72, 1.37)	0.655
<1.1 $\times$ 10^9/L, n (%)	146 (56.6)	30 (47.6)	116 (59.5)	0.099
Lymphocyte percentage (%), median (IQR)	18.4 (11.63, 26.08)	16.4 (9.05, 25.1)	18.65 (12.3, 26.7)	0.118
<20%, n (%)	150 (58.1)	41 (65.1)	109 (55.9)	0.199
NLR, median (IQR)	3.95 (2.47, 7.07)	4.56 (2.69, 9.51)	3.8 (2.25, 6.31)	0.043
Eosinophil ($\times10^9$/L), median (IQR)	0.03 (0, 0.07)	0.02 (0, 0.08)	0.03 (0, 0.07)	0.553
<0.02 $\times$ 10^9/L, n (%)	111 (43.0)	29 (46.0)	82 (42.1)	0.579
CRP (mg/L), median (IQR)	30.75 (4.94, 69.17)	30.75 (4.53, 81.72)	30.68 (5.75, 67.37)	0.765
PCT (ng/ml), median (IQR)	0.07 (0.05, 0.14)	0.07 (0.05, 0.26)	0.07 (0.04, 0.13)	0.116
LDH (U/L), median (IQR)	268.5 (206, 355.75)	318 (195.5, 426.3)	264.5 (207, 338)	0.205
FBG (mmol/L), median (IQR)	6.04 (5.41, 7.20)	7.54 (6.37, 10.62)	5.81 (5.32, 6.59)	<0.001
CREA (μmol/L), median (IQR)	69.6 (57.93, 79.9)	74 (64.25, 95.78)	67.8 (57.2, 78.23)	0.005
BUN (mmol/L), median (IQR)	4.65 (3.66, 6.34)	5.9 (4.09, 8.62)	4.41 (3.58, 5.57)	<0.001
CK-MB (U/L), median (IQR)	12 (9, 15)	14 (10, 17)	11 (9, 14)	0.042
D-Dimer (μg/mL), median (IQR)	0.56 (0.27, 1.62)	0.87 (0.35, 2.46)	0.54 (0.25, 1.51)	0.046
PT (sec), median (IQR)	13 (12.3, 13.9)	12.05 (12.8, 14)	13(12.4, 13.9)	0.394
APTT (sec), median (IQR)	36.75 (33.45, 40.65)	37 (32.55, 42.55)	36.6 (33.65, 40.5)	0.760
TT (sec), median (IQR)	15.6 (14.93, 16.3)	16.1 (15.25, 16.65)	15.5 (14.9, 16.23)	0.035
INR, median (IQR)	1 (0.94, 1.09)	0.98 (0.91, 1.1)	1 (0.94, 1.09)	0.326
Abnormal Chest CT images, n (%)	254 (98.4)	62 (98.4)	192 (98.5)	0.978
Bilateral lung involved	247 (95.7)	60 (95.2)	187 (95.9)	
Left lung involved only	3 (1.2)	1 (1.6)	2 (1.0)	
Right lung involved only	4 (1.6)	1 (1.6)	3 (1.5)	

DM, diabetes mellitus; IQR, interquartile range; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase; FBG, fasting blood glucose; CREA, serum creatine; BUN, blood Urea nitrogen; CK-MB, creatine kinase isoenzyme MB; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; INR, international normalized ratio.

Table 3 – Disease severity, treatment, and prognosis of COVID-19 patients.

Variable	Total (N = 258)	DM (n = 63)	Non-DM (n = 195)	P
Severity, n (%)				
Mild to moderate	87 (33.7)	18 (28.6)	69 (35.4)	0.028
Severe	116 (45.0)	24 (38.1)	92 (47.2)	
Critical	55 (21.3)	21 (33.3)	34 (17.4)	
Complications, n (%)				
Acute respiratory distress	62 (24.0)	24 (38.1)	38 (19.5)	0.001
Acute cardiac injury	19 (7.4)	9 (14.5)	10 (5.1)	0.016
Acute kidney injury	7 (2.7)	3 (4.8)	4 (2.1)	0.250
Medication, n (%)				
Antiviral agent	246 (95.3)	60 (95.2)	186 (95.4)	0.962
Antibiotic	162 (62.8)	47 (74.6)	115 (59.0)	0.026
Corticosteroid	74 (28.7)	17 (27.0)	57 (29.2)	0.792
Oxygen support, n (%)				
Nasal cannula	148 (57.4)	30 (47.6)	118 (60.5)	0.037
High-flow oxygen	24 (12.4)	8 (12.7)	24 (12.3)	
Non-invasive ventilation	26 (10.1)	10 (15.9)	16 (8.2)	
Invasive mechanical ventilation	16 (6.2)	7 (11.1)	9 (4.6)	
ECMO	1 (0.4)	1 (1.6)	0 (0)	
Prognosis, n (%)				
Discharged	87 (33.7)	16 (35.7)	71(36.4)	0.039
Not discharged yet	156 (60.5)	40 (63.5)	116 (59.5)	
Death	15 (5.8)	7 (11.1)	8 (4.1)	

DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation.

Table 4 – Associations of diabetes and FBG with fatality of COVID-19 in Cox proportion hazard models.

Variable	Model I [a]		Model II [b]		Model III [c]	
	AHR (95%CI)	P	AHR (95%CI)	P	AHR (95%CI)	P
DM	2.80 (1.01,7.80)	0.048	2.84 (1.01, 8.01)	0.048	3.64 (1.09, 12.21)	0.036
FBG (mmol/L)	1.14 (1.06,1.22)	<0.001	1.14 (1.07, 1.23)	<0.001	1.19 (1.08, 1.31)	<0.001

AHR, adjusted hazard ratio; CI: confidence interval. DM: diabetes mellitus; FBG: fasting blood glucose.
[a] Adjusted for age.
[b] Additionally adjusted for preexisting cardiovascular disease and chronic kidney disease.
[c] Additionally adjusted for inflammatory biomarkers (leucocytes, neutrophils, lymphocyte, eosinophil, NLR, neutrophil-to-lymphocyte ratio; C-reactive protein, procalcitonin).

To the best of our knowledge, this study was the first to investigate the clinical characteristics and prognosis of COVID-19 patients with diabetes. The prevalence of diabetes mellitus is sharply climbing in China in the last few decades. According to the latest nationally representative cross-sectional survey in mainland China in 2013, the estimated prevalence of diabetes in elderly participants (≥60 years old) was 20.2% [4]. Previous studies reported 9% to 14% prevalence of diabetes in COVID-19 patients [1,8,14,16]. Here, we reported a higher prevalence rate of diabetes in these patients, which might be due to the larger proportion of geriatric patients infected by SARS-CoV-2 in our study. The median age of all the participants was 64 years old, which was older than the data previously reported [1,7,8]. In the current study, 53.5% of the patients were male, and the percentage is similar to that reported by Wang et al [8] and Zhang et al [16]. Besides diabetes mellitus, hypertension (38.0%) and cardiovascular diseases (15.1%) were also common underlying chronic illness, and COVID-19 patients with diabetes seemed to have more comorbidities of cardiovascular diseases and chronic kidney diseases in the current study.

The laboratory findings on admission showed that leucocytes and neutrophils count and the proportion of increased leucocytes were higher in COVID-19 patients with diabetes than those without, which might be explained by the fact that patients with diabetes were more susceptible to pathogens after a viral infection due to lower immune function. During hospitalization, patients with diabetes were more likely to receive antibiotic therapy as well. Decreased lymphocytes count and eosinophil count were also common in these patients; this was consistent with the results of previous studies [16]. However, no significant differences were found in the cell counts and percentage lymphocytes and eosinophil count between COVID-19 patients with or without diabetes. The data revealed that COVID-19 patients with diabetes had a higher NLR, which was recently reported as a predictor of severity of COVID-19 in the early stage [17].

We found that COVID-19 patients with diabetes were more likely to develop severely or critically ill subtypes, including more complications with ARDS, acute cardiac injury, resulting in receiving more antibiotic therapy and mechanical ventilation. Cox regression model indicated that both diabetes and FBG level on admission were independent predictors for the fatality of COVID, after adjusting for potential confounders. Based on these findings, we diligently concluded that diabetes was associated with deteriorating disease severity and worsening prognosis in patients with COVID-19.

This is the first report to demonstrate that diabetes was associated with aggravating disease severity and poorer prognosis in COVID-19 patients. An increasing number of studies have shown that patients with diabetes have had higher mortality and morbidity of severe medical illness, such as myocardial infarction. High FBG plays an independent predictive role in hospitalized critically ill patients than those without diabetes as well [18–20]. Diabetes has also been identified as a significant risk factor for severe disease following respiratory tract infections [21]. Several studies demonstrated that diabetes was associated with increased risks of severity and mortality after SARS-CoV and MERS-CoV infection [22–25], and FBG level was an independent predictor for fatality in patients with SARS [22]. A very recent study indicated that well-controlled glycemia was associated with markedly improved outcomes of COVID-19 patients combined with pre-existing T2D [26].

Additionally, we found that COVID-19 patients with diabetes also had preexisting cardiovascular disease, and were more susceptible to having acute cardiac injury during hospitalization, which might increase the possibility of short-term poor prognosis in patients with diabetes after SARS-CoV-2 infection. Previous studies reported that patients with diabetes who received intensive glycemic control had lower risk of cardiovascular events [27]. Nevertheless, we could conclude that diabetes and FBG were independent predictive risks for poor outcomes in COVID-19 patients after adjusting those confounders and mediators.

Diabetes results in a proinflammatory homeostatic immune response skewed toward helper T cell 1 (Th1) and T17 cells and a decrease in regulatory T cells (Treg) [6]. Immune dysfunction of diabetes alone or following infection has been reported for a wide variety of immune cells, not just macrophages, monocytes and $CD4^+$ T cells [6]. A recent study reported the number of total T cells, $CD4^+$ and $CD8^+$T cell subsets were substantially reduced and functionally exhausted in COVID-19 patients, especially among geriatric and critically ill patients who required ICU admission [28]. Kulcsar KA *et al* showed that diabetic mice presented a prolonged phase of severe disease and delayed recovery after MERS-CoV infection, which was attributed to dysregulated immune response with lower inflammatory monocytes/macrophages and $CD4^+$ T cells [29]. Thus, optimal management of diabetes and intensive glycemic control may help prevent the occurrence of life-threatening infections and complications associated with diabetes mellitus, as well as to combat the increased susceptibility of infections due to impaired cellular and humoral immunity.

5. Limitations

Our study was subject to a few limitations that should not go unnoticed. Firstly, this study was a retrospective study, so we included a very small proportion of patients with laboratory-confirmed SARS-CoV-2 infection in Wuhan. Berkson bias might be introduced since asymptomatic patients and those with mild symptoms were less likely to be enrolled. Secondly, due to the massive number of patients and the lack of medical resources, the interval from the onset of the illness to hospital admission was more than 10 days for most patients, which could further complicate and deteriorate their condition. Nevertheless, patients with diabetes had a similar interval from onset of illness to hospital admission compared with those without diabetes. Thirdly, at the time of the study submission, most of the patients were not discharged yet, and the final survival outcome could not have been determined, and the long-term prognosis was not observed. Fourthly, other diabetes-associated parameters, including glycated hemoglobin, "peak levels" or "postprandial levels" of plasma glucose could better reflect the association of plasma glucose control and mortality in patients with COVID-19 if that data was available.

6. Conclusions

In the current study, we demonstrated that diabetes mellitus is associated with greater disease severity and poorer short-term outcomes including death. Stronger personal prophylactic strategies are advised for patients with diabetes, and more intensive surveillance and treatment should be considered when they are infected with SARS-CoV-2, especially for geriatric patients or those with preexisting comorbidities.

Funding

This study was supported by Emergency Project of Prevention and Control for COVID-19 of Central South University (No. 160260004); Project of Special Program on COVID-19 of Changsha Technology Hall (No. kq2001049); Science and technology innovation project of Hunan Province (No. S2018SFYLJS0108); National Key R&D Program of China (No. 2016YFC1304204).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We thank all the patients involved in the study. We thank all the medical staff who are fighting against this public crisis. We also thank Dr. Abira Afzal Choudhry for proofreading this paper.

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