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

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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.
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 epicenter 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 ≥30/min; (2) Pulse oximeter oxygen saturation ≤93% at rest; (3) Oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2) ≤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-
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] × 10⁹/L vs. median: 5.45[IQR: 4.31, 7.19] × 10⁹/L, P = 0.039) and median neutrophils count (median: 4.49[IQR: 3.12, 6.91] × 10⁹/L vs. median: 3.82[IQR: 2.81, 5.39] × 10⁹/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...
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] lmol/L vs. median: 67.8 [IQR: 57.2, 78.23] lmol/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 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.
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 poor prognosis in patients with COVID-19 [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.
The current study 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.

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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.

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