Abnormal Glucose Metabolism Leads To Severe COVID-19 Due To Hyperinflammation: A Cross-Sectional Study

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Abstract

**Background:** We aimed to describe the clinical features of novel coronavirus disease 2019 (COVID-19) patients with or without diabetes, focusing on the effect of abnormal HbA1c levels on inflammatory reactions and disease severity.

**Methods:** A total of 190 patients with COVID-19 were included in this cross-sectional study. Clinical and laboratory characteristics were collected and compared among moderate, severe, and critical cases, as well as among diabetes, prediabetes and nondiabetes cases. Receiver operating characteristic (ROC) curves were constructed to determine the diagnostic ability of HbA1c for disease severity. Logistic regression was used to explore the relationship between HbA1c levels and worse prognosis of COVID-19.

**Results:** HbA1c levels at admission were significantly different in patients with moderate, severe, and critical diseases (P<0.001). The area under the curve (AUC) of HbA1c levels to distinguish between moderate and severe-critical diseases was 0.938 (95% CI 0.906–0.970). After adjustment for confounders, the results showed that the increasing odds of in-hospital deaths were associated with HbA1c levels >6.0% (42 mmol/mol) (aOR 2.971 [95% CI 1.002, 8.804], P=0.049), and the increasing odds of severe or critical COVID-19 were associated with HbA1c levels ≥5.7% (39 mmol/mol) (aOR 29.588 [95% CI 8.285, 105.457], P<0.001). In addition, HbA1c levels strongly correlated with inflammatory markers and cytokines.

**Conclusions:** Abnormal glucose metabolism can cause a hyperinflammatory state of COVID-19, which manifests as severe disease.

Background

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first discovered in Wuhan, China, in December 2019 [1, 2]. The clinical spectrum of COVID-19 pneumonia ranges from mild to critical cases, and the risk factors associated with the development of more severe cases and deaths include older age, neutrophilia, organ dysfunction, coagulopathy, and elevated D-dimer levels [3]. In addition, multiple studies have revealed a grim reality that diabetes is already the top three common complications of COVID-19. Among patients with confirmed COVID-19, the proportion with comorbid diabetes was 33.8% in a study of 5,700 patients [4], 16.2% in a study of 1,099 patients [2], and 8.2% in a study of 1,590 patients [5]. Notably, several studies have already suggested that diabetes constitutes a higher proportion of patients with severe and ICU-admitted cases of COVID-19 than with mild cases [6-9]. Glycated hemoglobin A1c (HbA1c) has been used as a measure of diabetes control and a parameter in relation to the risk of complications [10]. In this study, we aimed to describe the clinical features of COVID-19 patients with or without abnormal glucose metabolism, focusing on the effect of abnormal HbA1c levels on inflammatory reactions and disease severity.

Methods

**Study Design and Participants**

This retrospective cross-sectional study enrolled 190 patients hospitalized in the Zhongfa district of Tongji Hospital in Wuhan from January 28, 2020. Outcome data, as discharged from or died in the hospital, were updated on March 25, 2020. The lowest period of follow-up was 28 days. Definitive cases of COVID-19 were diagnosed by positive RT-qPCR results from pharyngeal swab specimens. The diagnosis was based on the criteria described in the Guidelines for Diagnosis and Treatment of COVID-19 (5th version) issued by the National Health Commission of China.

The study was approved by the Ethics Commission of the Second Hospital of Jilin University (No. 2020052). Given the urgency of the COVID-19 pandemic, the requirement for informed consent was waived by the Ethics Commission.

**Data Collection**

Medical records of COVID-19 patients were reviewed, and medical histories, clinical symptoms, chest computed tomography (CT) images, laboratory examinations, and outcome data were collected. Laboratory examinations included
HbA1c, routine blood tests, kidney function, liver function, tissue damage, infection (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], procalcitonin [PCT], and serum ferritin [SF]), cytokines (interleukin-1 [IL-1], interleukin-2R [IL-2R], interleukin-6 [IL-6], interleukin-8 [IL-8], interleukin-10 [IL-10] and tumor necrosis factor-α [TNF-α]), immunoglobulins (IgA, IgG, and IgM), and complement proteins (C3 and C4). The above data were collected on the second day after admission. Two doctors independently reviewed the data collection form to ensure accuracy.

**Definitions**

Diabetes was defined according to the guidelines of the American Diabetes Association. Patients with HbA1c levels ≥ 6.5% (48 mmol/mol) were diagnosed with diabetes, and 5.7-6.4% (39-47 mmol/mol) were defined as prediabetes.

Disease severities were classified as mild, moderate, severe, and critical, according to the Guidelines for the Diagnosis and Treatment of COVID-19. Mild type: mild clinical symptoms and no abnormal radiological findings. Moderate type: fever, cough and other symptoms presented with pneumonia on chest CT. Severe type: one of the following conditions is met: oxygen saturation on room air at rest ≤ 93%; partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤ 300 mmHg; respiratory rate ≥ 30 per min. Critical type: one of the following conditions is met: shock occurs; patients with respiratory failure requiring mechanical ventilation; patients with other organ dysfunction requiring intensive care unit monitoring treatment. In this study, we enrolled patients with moderate, severe, and critical disease, judged at the time of admission.

**Statistical Analysis**

All measurements were nonnormally distributed according to the Kolmogorov–Smirnov test. Continuous and categorical variables are presented as medians (IQRs) and n (%), respectively. We used the Kruskal–Wallis test, Mann–Whitney U test, chi-square test, or Fisher’s exact test to compare differences between moderate, severe, and critical cases, as well as between diabetes, prediabetes and nondiabetes cases. The correlation between HbA1c levels and other laboratory examinations was evaluated by Spearman’s rank correlation coefficient. We constructed receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC) to determine the diagnostic ability of HbA1c for disease severity. The optimal cutoff was defined as the one maximizing Youden’s index. Multivariate logistic regression was used to estimate the relationship between HbA1c levels and in-hospital deaths and severe or critical COVID-19. The adjusted odds ratio (aOR) and 95% confidence interval (95% CI) were calculated as the risk estimate. All data analyses were carried out using IBM SPSS Statistics (Version 25.0) and R software (Version 3.6.0).

**Results**

**Demographics and Characteristics of the Study Population**

A total of 190 patients with COVID-19 were included in this study, of whom 69 were moderate, 80 were severe, and 41 were critical. The median age was 59.5 years (IQR 46.8–69.0 years), ranging from 14 years to 86 years, and 102 patients (53.7%) were male. The duration from first symptoms to hospital admission was 10.0 days (IQR 6.0–14.0 days). The most common onset symptoms were fever (161 patients [84.7%]), cough (137 patients [72.1%]), and fatigue (126 patients [66.3%]). Hypertension (58 patients [30.5%]), diabetes (53 patients [27.9%]), and cardiovascular disease (21 patients [11.1%]) were the most common comorbidities. Thirty-two patients (16.8%, 2 were severe type, and 30 were critical type) died during hospitalization, and 158 patients (83.2%) were successfully treated and discharged. Among the 32 deaths, 96.9% (31 patients) had abnormal blood glucose metabolism.

**Relationship Between Glucose Metabolism and Disease Severity in COVID-19**

We retrospectively analyzed the clinical data of 190 confirmed COVID-19 cases with diabetes, prediabetes or nondiabetes (Table 1). We found that patients with abnormal glucose metabolism were more severely ill and had significantly higher mortality than patients with normal glucose metabolism. Furthermore, we found that patients with different severities of COVID-19 had significantly different HbA1c levels at admission (Fig. 1A). The mean HbA1c levels of patients with moderate, severe, and
critical diseases were 5.9% ([IQR 5.5–6.2%], or 41 mmol/mol [IQR 37–44]), 6.1% ([IQR 5.8–6.7%], or 43 mmol/mol [IQR 40–50]), and 6.4% ([IQR 6.0–6.8%], or 46 mmol/mol [IQR 42–51]), respectively. To test the ability of HbA1c levels to diagnose severe and critical diseases, we used the ROC curve to analyze the optimal prediction threshold of COVID-19 exacerbation. The AUC of HbA1c levels to distinguish between moderate and severe-critical diseases was 0.938 (95% CI 0.906–0.970), and the HbA1c level cut off of 6.0% (42 mmol/mol) had 80.2% sensitivity and 100% specificity (Fig. 1B). The AUC of HbA1c levels to distinguish between moderate-severe and critical diseases was 0.792 (95% CI 0.727–0.856), and the HbA1c level cutoff of 6.0% (42 mmol/mol) had 97.6% sensitivity and 61.7% specificity (Fig. 1C). Moreover, we performed logistic regression to identify risk factors associated with in-hospital deaths and severe or critical COVID-19 in this cohort. After adjustment for confounders (consolidation in CT images, PCT, IL-2R, IL-6, IL-10, C4), the results showed that increasing odds of in-hospital deaths were associated with HbA1c levels >6.0% (42 mmol/mol) (aOR 2.971 [95% CI 1.002, 8.804], P=0.049, Table 2), and increasing odds of severe or critical COVID-19 were associated with HbA1c levels ≥ 5.7% (39 mmol/mol) (aOR 29.588 [95% CI 8.285, 105.457], P<0.001, Table 3). Based on clinical experience, we conducted a subgroup analysis of different ages and sexes. The results suggested that HbA1c levels >6.0% (42 mmol/mol) were an independent risk factor for in-hospital deaths in those <60 years (aOR 16.063 [95% CI 1.172, 220.100], P=0.038, Table 2)
Table 1-Characteristics, radiological findings, outcomes and Inflammation related laboratory examinations of COVID-19 patients with different levels of HbA1c.

|                              | Total (n=190) | Non-diabetes (n=39) | Pre-diabetes (n=98) | Diabetes (n=53) | P value |
|------------------------------|--------------|---------------------|---------------------|----------------|---------|
| **Age, years**               | 59.5 (46.8, 69.0) | 43.0 (32.0, 52.0) | 62.0 (53.0, 69.0) | 63.0 (55.0, 70.0) | <0.001 |
| **Gender**                   |              |                     |                     |                | 0.053   |
| Male                         | 102 (53.7)  | 16 (41.0)           | 51 (52.0)           | 35 (66.0)      | -       |
| Female                       | 88 (46.3)   | 23 (59.0)           | 47 (48.0)           | 18 (34.0)      | -       |
| **BMI, kg/m^2**              | 24.6 (23.3, 26.5) | 24.0 (22.4, 25.7) | 24.6 (23.4, 26.4) | 25.3 (23.6, 28.2) | 0.047   |
| **SaO2, %**                  | 91.0 (89.0, 94.0) | 94.0 (91.0, 95.0) | 91.0 (89.0, 94.0) | 90.0 (86.0, 92.5) | <0.001 |
| **Mechanical ventilation**   | 41 (21.6)   | 3 (7.7)             | 19 (19.4)           | 19 (35.8)      | <0.001 |
| **Disease severity**         |              |                     |                     |                | <0.001  |
| Moderate                     | 69 (36.3)   | 25 (64.1)           | 35 (35.7)           | 9 (17.0)       | -       |
| Severe                       | 80 (42.1)   | 11 (28.2)           | 44 (44.9)           | 25 (47.2)      | -       |
| Critical                     | 41 (21.6)   | 3 (7.7)             | 19 (19.4)           | 19 (35.8)      | -       |
| **Death**                    | 32 (16.8)   | 1 (2.6)             | 16 (16.3)           | 15 (28.3)      | 0.005   |
| **Distribution**             |              |                     |                     |                | <0.001  |
| Unilateral                   | 20 (10.5)   | 12 (30.8)           | 7 (7.1)             | 1 (1.9)        | -       |
| Bilateral                    | 170 (89.5)  | 27 (69.2)           | 91 (92.9)           | 52 (98.1)      | -       |
| GGO                          | 102 (53.7)  | 18 (46.2)           | 53 (54.1)           | 31 (58.5)      | 0.500   |
| Patch shadow                 | 127 (66.8)  | 22 (56.4)           | 65 (66.3)           | 40 (75.5)      | 0.157   |
| Fiber cord shadow            | 38 (20.0)   | 7 (17.9)            | 19 (19.4)           | 12 (22.6)      | 0.837   |
| Consolidation                | 29 (15.3)   | 5 (12.8)            | 11 (11.2)           | 13 (24.5)      | 0.085   |
| **Laboratory parameters**    |              |                     |                     |                |         |
| HbA1c level, %               | 6.1 (5.7, 6.6) | 5.5 (5.4, 5.6) | 6.0 (5.9, 6.2) | 7.1 (6.7, 8.6) | <0.001 |
| WBC, ×10^9/L                 | 5.3 (4.0, 7.7) | 4.5 (3.4, 6.2) | 5.2 (3.9, 7.5) | 7.0 (5.1, 7.0) | <0.001 |
| Neutrophile ratio, %         | 70.4 (62.2, 83.7) | 67.2 (51.5, 70.7) | 70.8 (62.8, 83.3) | 76.6 (66.1, 88.0) | <0.001 |
| Lymphocyte ratio, %          | 19.2 (11.4, 27.3) | 23.6 (17.4, 35.0) | 18.9 (13.0, 27.6) | 14.5 (6.9, 14.5) | <0.001 |
| Eosinophile ratio, %         | 0.1 (0.0, 0.6) | 0.3 (0.1, 1.1) | 0.2 (0.0, 0.6) | 0 (0, 0)       | 0.139   |
| **Inflammatory markers**     |              |                     |                     |                |         |
| ESR, mm/H                    | 26.5 (12.0, 34.0) | 13.0 (7.0, 34.0) | 25.5 (12.0, 41.0) | 35.0 (21.5, 58.0) | <0.001 |
42.3)

| Variable   | Median (IQR)     |
|------------|------------------|
| CRP, mg/L  | 30.5 (5.4, 72.8) |
|            | 18.6 (2.1, 41.8) |
|            | 28.7 (7.9, 69.3) |
|            | 49.8 (10.5, 106.0) |
| PCT, ng/mL | 0.1 (0.0, 0.1)   |
|            | 0 (0.0, 0.1)     |
|            | 0.1 (0.0, 0.1)   |
|            | 0.1 (0.0, 0.2)   |
| SF, ug/L   | 610.3 (289.4, 1153.1) |
|            | 320.7 (105.5, 683.4) |
|            | 617.3 (291.1, 1157.6) |
|            | 888.1 (473.9, 1268.6) |
| Cytokines  |                 |
| IL-2R, U/ml | 674.0 (459.0, 1000.8) |
|            | 429.0 (335.0, 679.0) |
|            | 663.5 (508.5, 957.5) |
|            | 805.0 (567.0, 1174.5) |
| IL-6, pg/mL | 14.7 (4.2, 48.6) |
|            | 11.3 (2.4, 21.8) |
|            | 16.6 (3.8, 50.0) |
|            | 22.5 (6.5, 61.7) |
| IL-8, pg/mL | 17.6 (9.6, 32.3) |
|            | 15.1 (9.4, 27.5) |
|            | 16.5 (9.5, 31.0) |
|            | 24.1 (9.4, 47.5) |
| TNF-α, pg/mL | 8.2 (6.3, 10.3) |
|            | 7.4 (5.3, 10.7) |
|            | 7.9 (6.2, 9.9) |
|            | 8.3 (6.9, 11.6) |

Data are expressed as median (IQR), n (%). Boldface P values are statistically significant (P < 0.05). BMI, Body Mass Index. GGO, Ground-glass opacity. PCT, procalcitonin. SF, serum ferritin.

Table 2-Logistic regression analysis for prediction of in-hospital deaths

| Variables                      | Total (n=190) | Subgroup analysis by age | Subgroup analysis by gender |
|-------------------------------|---------------|--------------------------|----------------------------|
|                               |               | <60 y (n=95)             | ≥60 y (n=95)               | Male (n=102) | Female (n=88) |
|                               | aOR (95% CI)  | P value                  | aOR (95% CI)               | P value      | aOR (95% CI)  | P value |
| Hb1Ac ≥6.0%                   | 2.971 (1.002, 8.804) | **0.049**               | 16.063 (1.172, 220.100)  | **0.038**   | 1.093 (0.288, 4.144) | 0.896 |
| Consolidation in CT images    | 5.796 (1.774, 18.936) | 0.004                    | 5.071 (0.406, 63.396)     | 0.208       | 6.477 (1.431, 29.312) | 0.015 |
| PCT ≥0.05 ng/mL               | 38.464 (2.708, 546.316) | 0.007                    | -                          | 0.997       | 16.205 (1.023, 256.703) | 0.048 |
| IL-6 ≥7.0 pg/ml               | 10.324 (1.998, 53.348) | 0.005                    | 13.199 (0.505, 345.319)   | 0.121       | 9.372 (0.947, 92.773) | 0.056 |
| IL-10 ≥9.1 pg/ml              | 5.145 (1.901, 13.927) | 0.001                    | 9.639 (0.731, 127.156)    | 0.085       | 4.559 (1.295, 16.054) | 0.018 |
| Complement-C4 ≥0.16 g/L       | 4.037 (1.285, 12.684) | 0.017                    | 4.960 (0.489, 50.271)     | 0.175       | 3.373 (0.776, 14.658) | 0.105 |

Variables with a p value < 0.01 in univariate analysis were included in multivariate analysis. Boldface P values are statistically significant (P < 0.05). aOR, adjusted odds ratio. CI, confidence interval. PCT, procalcitonin.
Table 3-Logistic regression analysis for prediction of severe or critical COVID-19

| Variables                          | Total (n=190) | Subgroup analysis by age | Subgroup analysis by gender |
|------------------------------------|---------------|--------------------------|-----------------------------|
|                                    |               | ≥60 y (n=95)             | Male (n=102)                | Female (n=88)               |
|                                    | aOR (95% CI) | P value                  | aOR (95% CI)               | P value                     | aOR (95% CI) | P value | aOR (95% CI) | P value |
| HbA1c≥5.7%                         | 29.588 (8.285, 105.457) | **0.001**               | 23.802 (4.298, 131.809)    | **0.001**                 | 49.403 (4.083, 597.703) | **0.002** | 19.801 (3.140, 124.841) | **0.001** | 38.074 (5.908, 245.370) | **0.001** |
| Consolidation in CT images         | 3.048 (0.776, 11.972)      | 0.110                    | 1.910 (0.246, 14.848)      | 0.536                      | 3.592 (0.393, 32.849)      | 0.257     | 2.971 (0.437, 20.178)     | 0.265   | 2.542 (0.354, 18.232)      | 0.354   |
| PCT≥0.05 ng/mL                     | 2.861 (1.200, 6.823)       | 0.018                    | 1.669 (0.494, 5.638)       | 0.409                      | 6.338 (1.707, 23.533)      | 0.006     | 4.579 (1.276, 16.436)     | 0.020   | 1.878 (0.541, 6.520)       | 0.321   |
| IL-2R710 U/ml                      | 11.138 (3.947, 31.431)     | **0.001**               | 24.265 (4.934, 119.342)    | **0.001**                 | 4.550 (1.082, 19.133)      | 0.039     | 11.495 (2.933, 45.051)    | **0.001** | 11.491 (2.156, 61.248)     | 0.004   |

Variables with a p value < 0.01 in univariate analysis were included in multivariate analysis. Boldface P values are statistically significant (P < 0.05). aOR, adjusted odds ratio. CI, confidence interval. PCT, procalcitonin.

Previous studies suggested that males were more likely to have severe or critical disease than females in COVID-19, and this significant difference between genders may be related to men being more likely to be current smokers and having a higher proportion of comorbid conditions [11]. Our research also confirmed the existence of this significant difference between sexes (P=0.004). To explore the possible causes, we further compared the HbA1c levels in male and female patients. Our data showed that HbA1c levels were significantly higher in male patients (P=0.023), which may be one of the factors that causes male patients to be more seriously ill.

Because of immune dysfunction, obesity and, more importantly, disproportionate body fat distribution could cause an even higher risk of severe outcomes. We analyzed body mass index (BMI) in our cohort and found that there was no significant relationship between BMI and in-hospital deaths (P=0.195).

At the same time, our data showed that chest CT images of patients with abnormal glucose metabolism were significantly more common with bilateral lung involvement and consolidation than normal glucose metabolism. Therefore, we further compared the HbA1c levels in patients with different radiological findings, and our data showed that both patients with bilateral pneumonia (P<0.001) and with consolidation (P=0.0013) in CT images had significantly higher levels of HbA1c. Additionally, we found that the rates of bilateral lung involvement (P<0.001) and consolidation (P=0.0021) were significantly different in moderate, severe, and critical patients. Hence, we concluded that COVID-19 patients with higher levels of HbA1c often had bilateral pneumonia and consolidation in CT images, and these radiological findings were also more common in seriously ill patients.

**Abnormal Glucose Metabolism Exacerbates Inflammation in COVID-19**

COVID-19 can manifest as viral-induced hyperinflammation and an inflammatory cytokine storm, causing patients to experience rapid deterioration. Therefore, we analyzed inflammation-related laboratory examinations of COVID-19 patients with diabetes, prediabetes or nondiabetes (Table 1).

First, we found that diabetes patients, when compared to prediabetes patients, showed significantly increased white blood cell counts and neutrophil ratios and significantly decreased lymphocyte ratios and eosinophil ratios. This significant difference also existed between prediabetes and nondiabetes patients. At the same time, our data showed a significant difference in white blood cell counts, neutrophil ratios, lymphocyte ratios, and eosinophil ratios between patients with moderate, severe, and critical
diseases (Fig. 2A), which prompted us to further analyze the potential relation of HbA1c levels with these cells. We evaluated the correlation by Spearman's rank correlation coefficient, and we found that the HbA1c levels positively correlated with white blood cell counts and neutrophil ratios and inversely correlated with lymphocyte ratios (Fig. 2B).

Second, we found that diabetes and prediabetes patients showed significantly increased levels of ESR, CRP, PCT, and SF, and these inflammatory markers can reflect the infection and determine the risk of septic shock. We further compared the levels of inflammatory markers, including ESR, CRP, PCT, and SF, between moderate, severe, and critical patients. All the above markers were significantly different between patients with different disease severities (Fig. 3A). Correlation analysis demonstrated that HbA1c levels positively correlated with ESR, CRP, PCT, and SF levels (Fig. 3B).

Third, our data showed that the levels of IL-2R were significantly increased in diabetes and prediabetes patients. In some respects, severe COVID-19 can be regarded as a virus-induced hyperinflammatory condition due to a cytokine cascade [12], and we found that the levels of IL-2R, IL-6, IL-8, and TNF-α were significantly different in patients with moderate, severe, and critical diseases (Fig. 4A). Among these cytokines, the levels of IL-2R were positively and strongly correlated with HbA1c levels (Fig. 4B).

**Discussion**

Multiple studies have confirmed that people with diabetes are at risk for greater susceptibility to SARS-CoV-2 infections [8, 13-17]. At the same time, among people with diabetes, the risk of worse prognosis of COVID-19 is two- to threefold higher than among those without, even after adjustment for sociodemographic factors and comorbid conditions [18]. As early as more than 30 years ago, studies reported that hospitalization during the influenza epidemic was six times higher in people with diabetes than in those without diabetes [19]. Moreover, epidemiological studies also indicate that pre-existing diabetes is independently associated with poor outcomes for patients with Severe Acute Respiratory Syndrome [20], and type 2 diabetes is the primary comorbidity associated with severe Middle East Respiratory Syndrome Coronavirus infections [21].

A recent study involving 17 million adults has shown that HbA1c levels <7.5% (58 mmol/mol) are associated with a 30% increased risk of COVID-19-related death compared with people without abnormal glucose metabolism; moreover, HbA1c levels ≥7.5% (58 mmol/mol) are associated with a twofold increase in risk [22]. Given the urgency of finding solutions to this current crisis, the results of our research may assist in prognostication. To distinguish between moderate and severe critical COVID-19, the AUC of HbA1c levels at admission was as high as 0.938 (95% CI 0.906–0.970). Furthermore, after adjustment for confounders, increasing odds of in-hospital deaths were associated with HbA1c levels >6.0% (42 mmol/mol) (aOR 2.971 [95% CI 1.002, 8.804], P=0.049), and increasing odds of severe or critical COVID-19 were associated with HbA1c levels ≥5.7% (39 mmol/mol) (aOR 29.588 [95% CI 8.285, 105.457], P<0.001). At the same time, elevated HbA1c levels should be considered an independent risk factor for in-hospital deaths in young adults, especially for individuals younger than 60 years old. A meta-analysis has reported that the association between diabetes and a poor composite outcome is stronger in studies that included younger COVID-19 patients than in studies that included older COVID-19 patients, which is in line with our current results [23].

Several studies have examined the association of prior HbA1c level management before the onset of COVID-19 infection and the risk of poor outcomes. Population-based studies in Europe have shown that individuals with HbA1c levels of 9.0-9.9% (74.9-84.7 mmol/mol) have a one-third higher mortality rate than individuals with HbA1c levels of 6.5-7.0% (47.5-53.0 mmol/mol) measured in the months before COVID-19 hospitalization [24]. A cohort study using data from an Israeli integrated payer-provider health care organization, which includes more than 4.7 million people, suggests that a difference in HbA1c levels from 8.0% (63.9 mmol/mol) to 6.0% (42.1 mmol/mol) is associated with a 29.0% reduction in the risk of severe COVID-19 [25].

Thus, it is essential to establish the magnitude of the association between glycemic control and the severity of COVID-19 and to choose an appropriate HbA1c target for people with diabetes to reduce the risk of severe COVID-19. Except for diabetes, prediabetes (HbA1c levels 5.7-6.4% [38.8-46.4 mmol/mol]) is highly prevalent in most populations. More than half of the participants in our study had prediabetes, and 16.3% had in-hospital deaths, which was significantly higher than that of participants without abnormal glucose metabolism. Especially worrying is the fact that the majority of people globally
with prediabetes are unaware of their diagnosis [26]. Therefore, it is important to screen HbA1c levels at the time of COVID-19 hospital admission to identify those with prediabetes.

HbA1c is interpreted as an indicator of blood glucose control in the past three months, while fasting blood glucose at admission may represent a biomarker of systemic inflammation. A meta-analysis of 6386 COVID-19 patients relating hyperglycemia at admission suggests that the hyperglycemia group has increased mortality (OR = 3.45 [95% CI 2.26, 5.26]) and severe or critical complications (OR = 2.08 [95% CI 1.45, 2.99]) [27]. In addition, a large case series including 548 COVID-19 patients found that larger magnitude glucose fluctuation in the first week of admission presents a higher risk of mortality and acute respiratory distress syndrome (ARDS) incidence [28]. Unfortunately, fasting blood glucose measurements during admission were not recorded in our registry. More notably, new-onset hyperglycemia in COVID-19 patients without diabetes, which may suggest a bidirectional relationship between SARS-CoV-2 infection and diabetes, has been increasingly recognized as a common phenomenon. Recent studies suggest that newly diagnosed diabetes may confer an increased risk of poor prognosis than pre-existing diabetes in COVID-19 [29, 30]. Some case reports and in vitro experiments indicate that SARS-CoV-2 infection may promote pancreatic dysfunction, potentially leading to new-onset hyperglycemia [31-33]. Since HbA1c is not affected by acute infections, it can assist in the detection of newly diagnosed diabetes in COVID-19 patients, thereby improving the prognosis of these patients.

There is a pathophysiological explanation to support the association between diabetes and COVID-19 severity: diabetes is a proinflammatory state characterized by an exaggerated cytokine response. Previous studies have confirmed that COVID-19 patients with diabetes may have higher rates of leukocytosis, neutrophilia, lymphocytopenia, eosinopenia, and levels of IL-1β, IL-6, IL-8, TNF-α, CRP and SF than patients without diabetes [34-36]. At the same time, a meta-analysis including 10 studies of COVID-19 demonstrated that severe illness was associated with higher leukocyte counts and lower lymphocyte counts [37], and another meta-analysis including 16 studies demonstrated that severe patients had higher levels of IL-6, CRP, PCT, ESR and SF than nonsevere patients [38]. Our data confirm previous studies and show that IL-2R levels in patients with abnormal glucose metabolism are higher than those in patients with normal glucose metabolism, and these hyperinflammatory states are strongly associated with the severity of COVID-19. Moreover, there was a strong positive correlation of HbA1c levels with ESR, CRP, PCT, SF, and IL-2R levels. This indicates that patients with diabetes are more susceptible to an inflammatory cytokine storm, which leads to the rapid deterioration of COVID-19.

An interesting finding in our study is that HbA1c levels are moderately correlated with IL-6 and IL-8 levels and are not correlated with TNF-α levels. One possible explanation is that TNF-α, IL-6 and IL-8 are the main inflammatory cytokines derived from adipose tissue, and fat mass correlates significantly with TNF-α [39, 40]. In our cohort, unlike the results of other studies [41], a linear dose–response curve between BMI and severe outcomes of COVID-19 was not observed. This finding may help reveal potential mechanistic links between obesity and worsening COVID-19.

A recent study analyzing single-cell RNA sequencing datasets of COVID-19 patients showed that genetic ACE2 deletion resulted in the upregulation of proinflammatory cytokines containing IL-6 and TNF-α [42]. Another study involving 245 COVID-19 patients with chronic diseases showed that the poor prognosis of COVID-19 patients with diabetes may be due to low circulating ACE2 levels [43]. When further exploring its mechanism, other researchers found that this upregulation of ACE2 activity is driven by comorbidities but not by ACE2-Ang-(1-7)-MAS blockade [44, 45]. Moreover, a study involving 88 COVID-19 patients found a negative correlation between vitamin D and fasting blood glucose, neutrophil/lymphocyte ratio, CRP and IL-6, which suggests that vitamin D deficiency may be a potential pathophysiological mechanism of COVID-19 in patients with diabetes [46].

There are several limitations in this study. First, the study population only included 190 patients from a single hospital, which may not be sufficiently powered for all the analyses. Second, COVID-19 patients with mild disease were not admitted to our center, which may lead to a partial understanding of the disease. Third, our registry did not record fasting blood glucose measurements during admission. Last, we did not distinguish between type 1 diabetes and type 2 diabetes.

**Conclusions**
In conclusion, we suggest that individuals with abnormal glucose metabolism who are affected by COVID-19 present uncontrolled release of proinflammatory cytokines and have a high risk of in-hospital death. Moreover, assessing HbA1c levels to identify patients at higher risk of poor outcomes at admission may be helpful for the allocation of critically ill patients as well as a guide to improve treatment strategies for COVID-19.

**List Of Abbreviations**

- aOR: adjusted odds ratio
- ARDS: acute respiratory distress syndrome
- AUC: area under the receiver operating characteristic curve
- BMI: body mass index
- COVID-19: novel coronavirus disease 2019
- CRP: C-reactive protein
- CT: computed tomography
- ESR: erythrocyte sedimentation rate
- GGO: Ground-glass opacity
- HbA1c: glycated hemoglobin A1c
- IL: interleukin
- PCT: procalcitonin
- ROC: receiver operating characteristic
- SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
- SF: serum ferritin
- TNF-α: tumor necrosis factor-α

**Declarations**

**Ethical Approval and Consent to participate:** The study was approved by the Ethics Commission of the Second Hospital of Jilin University (No. 2020052). Given the urgency of the COVID-19 pandemic, the requirement for informed consent was waived by the Ethics Commission.

**Consent for publication:** Not applicable.

**Availability of supporting data:** The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

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Authors’ contributions: All authors contributed to this study. JY conceived and designed the study. BY, RG, JR, ZS, and TM acquired data. HL, RG, JR, ZS, and TM analyzed and interpreted data. HL, and JY wrote the article and revised it critically. JY is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Figures**
Figure 1

(A) The HbA1c levels were significantly different in COVID-19 patients with different disease severity. (B) ROC curves between moderate and severe-critical diseases. (C) ROC curves between moderate-severe and critical diseases.

Figure 2

(A) Levels of WBC, NR, LR, and ER. (B) The HbA1c levels in COVID-19 patients positively and strongly correlated with WBC, NR, and inversely correlated with LR. HbA1c: glycated hemoglobin A1c. WBC: white blood cell counts. NR: neutrophil ratios. LR: lymphocyte ratios. ER: eosinophil ratios. Numbers in the squares are "R" values. **P<0.001, *P<0.05.
Figure 3

(A) Levels of ESR, CRP, PCT, and SF. (B) The HbA1c levels in COVID-19 patients positively correlated with ESR, CRP, PCT, and SF levels. HbA1c: glycated hemoglobin A1c. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. PCT: procalcitonin. SF: serum ferritin. Numbers in the squares are “R” values. **P<0.001.

Figure 4
(A) Levels of IL-2R, IL-6, IL-8, and TNF-α. (B) The HbA1c levels in COVID-19 patients positively and strongly correlated with IL-2R levels. HbA1c: glycated hemoglobin A1c. IL-2R: interleukin-2R. IL-6: interleukin-6. IL-8: interleukin-8. TNF-α: tumor necrosis factor-α. Numbers in the squares are “R” values. **P<0.001, *P<0.05.