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Hyperglycemia is a strong predictor of poor prognosis in COVID-19

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ABSTRACT

Aims: The objective of this study is to explore the association between documented diabetes, fasting plasma glucose (FPG), and the clinical outcomes of Coronavirus disease 2019 (COVID-19).

Methods: This retrospective study included 255 patients with COVID-19. Of these, 214 were admitted to isolation wards and 41were admitted to intensive care units (ICUs). Demographic, clinical, treatment, and laboratory data were collected and compared between ICU and non-ICU patients. Multivariable logistic regression models were used to explore the risk factors associated with poor clinical outcomes (ICU admission or death).

Results: There were significant changes in several clinical parameters in ICU patients (leukopenia, lymphopenia, elevated D-dimer, as well as higher levels of FPG, cardiac troponin, serum ferritin, IL-6, and high-sensitivity C-reactive protein)compared with non-ICU patients. The prevalence of known diabetes was substantially higher in ICU than non-ICU patients (31.7% vs. 17.8%, P = 0.0408). Multivariable regression analysis showed that a history of diabetes [odds ratio (OR), 0.099; 95% confidence interval (CI), 0.016–0.627; P = 0.014], high FPG at admission (OR, 1.587; 95% CI, 1.299–1.939, P < 0.001), high IL-6 (OR, 1.01; 95% CI, 1.002–1.018, P = 0.013), and D-dimer higher than 1 mg/L at admission (OR, 4.341; 95% CI, 1.139–16.547, P = 0.032) were independent predictors of poor outcomes. Cox proportional hazards analysis showed that compared with FPG < 7 mmol/L, FPG levels of 7.0–11.1 mmol/L and ≥ 11.1 mmol/L were associated with an increased hazard ratio (HR) for poor outcome (HR, 5.538 [95% CI, 2.269–13.51] and HR, 11.55 [95% CI, 4.45–29.99], respectively).

Conclusion: Hyperglycemia and a history of diabetes on admission predicted poor clinical outcomes in COVID-19.

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1. Introduction

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in Wuhan, China [1]. The disease rapidly spread across the globe and was declared to be a public health emergency of international concern by the World Health Organization [2]. High-throughput sequencing revealed that SARS-CoV-2 belongs to the genus Betacoronavirus, with a nucleotide identify of 79.0% and 50.0% to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively [3–4]. The clinical spectrum of COVID-19 appears to be large, ranging from asymptomatic cases to severe disease, the latter being characterized by acute respiratory distress syndrome (ARDS), potentially leading to death [5–8]. The mechanisms behind severe pathology are not completely known. Therefore, the identification of risk factors for disease severity and prompt treatment are crucial.

COVID-19 patients who are elderly or present with comorbidities, including diabetes, obesity, and hypertension, usually have high morbidity and mortality [5–8]. Diabetes has become epidemic in China. A previous study indicated that the overall prevalence of prediabetes and diabetes was 35.7% and 10.9%, respectively [9]. Diabetes has been reported to downregulate the innate and humoral immune system by reducing the function of macrophages, lymphocytes, and neutrophils [10–11]. Patients with diabetes are more susceptible to a broad range of infections, including influenza virus, SARS, and MERS [12–14]. A recent study involving 1099 COVID-19 patients indicated that 16.2% patients with severe disease had diabetes [15]. Another study including 52 critically ill adult patients admitted to intensive care units (ICUs) found that 22% of non-survivors were diabetic. In addition, COVID-19 associated with diabetes had a higher potential to progress rapidly to ARDS, septic shock, and death [8].

The objective of this study is to investigate the association between a documented history of diabetes, fasting plasma glucose (FPG) levels, and clinical outcomes in COVID-19, and the effect of steroid therapy on plasma glucose during disease progression.

2. Methods

2.1. Study design and participants

Consecutive patients with confirmed COVID-19 admitted to the Zhongfaxincheng campus of Tongji Hospital were enrolled in the study from February 1, 2020 to February 24, 2020. All patients were diagnosed according to the WHO interim guidance [16] and were positive for SARS-CoV-2 by RT-PCR test. The research was approved by the institutional review board of our institution. Oral informed consent was obtained from all patients. All procedures were in accordance with the World Medical Association's Declaration of Helsinki.

According to Chinese government recommendations, non-severe patients with COVID-19 are admitted to "Fangcang" Field Hospital [17], whereas severe patients are assigned to the designated hospitals such as Tongji Hospital, which treats COVID-19 patients coming from other hospitals assigned by the government. Our cohort presented the following conditions: (1) inability to perform self-care or daily life activities; (2) respiratory rate $\geq$ 30 breaths per min or blood oxygen saturation $\leq$ 93% at rest; (3) severe comorbidities, including acute intracerebral hemorrhage, acute myocardial infarction, heart failure, acute cerebral infarction, renal failure, or malignant tumors.

Our cohort was treated according to the seventh edition of the Chinese Management Guideline for COVID-19 [18]. Clinical outcomes were followed up until March 31, 2020. The criteria for hospital discharge were absence of fever for at least 3 days, significant improvement in chest computed tomography and respiratory symptoms, and two negative RT-PCR results of nasopharyngeal swab samples collected at least 24 h apart. The main cumulative endpoint was referral to an ICU or death. Patients were admitted to ICUs in cases of (i) respiratory failure and need for mechanical ventilation; (ii) failure of other organs and need for intensive care.

2.2. Data collection

Data on epidemiological characteristics, clinical symptoms, laboratory results, treatments, and clinical outcomes were collected from medical records. Laboratory assessments at admission included complete blood count, coagulation profile, blood chemistry (renal and liver function, myocardial enzymes, lactate dehydrogenase, and electrolytes), cytokines (interleukin [IL]-6, IL-8, IL-10, and TNF-α), serum ferritin, and high-sensitivity C-reactive protein (hs-CRP).

2.3. Statistical analysis

Continuous variables were expressed as mean, median, and interquartile range. Independent group t-tests were used to compare the means of continuous variables for normally-distributed data, and the Mann-Whitney test was adopted for non-normally-distributed data. Categorical variables were described as frequencies and percentages. Differences in the distribution of categorical data were determined using Fisher's exact test or chi-square test. Multivariable logistic regression analysis was carried out to analyze the risk factors associated with poor outcomes (ICU admission or death). The Cox proportional hazards regression model was used to assess the effect of FPG levels on clinical outcomes in survival analysis. All statistical analyses were performed using SPSS version 13.0. All tests were two-tailed, and p-values of less than 0.05 were considered statistically significant.

3. Results

3.1. General characteristics of patients with COVID-19

A total of 255 COVID-19 patients were included in the study, and baseline characteristics are shown in Table 1. All patients resided in Wuhan City. Eighty-five (33.3%) patients had contact with SARS-CoV-2-positive patients, 45 (17.6%) patients were exposed to infected family members, and none visited live poultry markets.

Table 1 – Clinical presentation and laboratory findings of patients with COVID-19 on admission.

	Total (n = 255)	Non-ICU (n = 214)	ICU (n = 41)
Age (years)	64 (24–92)	64 (24–92)	64 (36–88)
Male (%)	136 (53.3%)	108 (50.9%)	28 (71.8%)*
Duration of hospitalization (days)	20 (5–51)	20 (6–48)	19 (5–51)
Duration of illness (days)	12 (3–34)	12 (5–30)	12 (3–34)
Comorbidity			
Hypertension (%)	101 (39.6%)	87 (40.7%)	14 (34.2%)
Diabetes (%)	51 (20.0%)	38 (17.8%)	13 (31.7%)*
Coronary heart disease (%)	28 (10.9%)	24 (11.2%)	4 (9.8%)
Chronic obstructive pulmonary disease (%)	8 (31.4%)	8 (3.7%)	3 (7.3%)
Other (%)	25 (9.8%)	19 (8.9%)	6 (14.6%)
Antiviral treatment (%)	207(81.2%)	174 (81.3%)	33 (80.5%)
Corticosteroid treatment (%)	69 (27.1%)	40 (18.7%)	29 (70.7%)**
White blood cell count ($\times 10^9$/L)	5.8 (2.2–20.8)	5.4 (2.2–15.8)	9.1 (2.4–20.8)***
Neutrophils ($\times 10^9$/L)	4.1 (1.1–18.9)	3.8 (1.1–13.7)	8.1 (1.8–18.9)***
Lymphocytes ($\times 10^9$/L)	0.9 (0.2–4.1)	1.1 (0.3–4.1)	0.6 (0.2–1.4)***
Platelets ($\times 10^9$/L)	212.0 (28.0–521.0)	217.0 (60.0–521.0)	186.0 (28.0–459.0)
Prothrombin time (s)	14.1 (10.6–23.6)	13.9 (10.6–18.7)	15.3 (12.8–95.0)***
D-dimer (mg/L)	1.2 (0.2–21.0)	0.99 (0.2–21.0)	6.8 (0.5–21.0)***
Albumin (g/L)	33.9 (17.2–65.9)	34.5 (23.9–65.9)	30.1 (17.2–69.3)***
Alanine aminotransferase (U/L)	25.0 (5.0–218.0)	24.0 (5–218.0)	34.0 (10.0–189.0)**
>40	60 (23.5%)	45 (21.0%)	15 (36.6%)*
Aspartate aminotransferase (U/L)	28.0 (10.0–392.0)	26.0 (10.0–392.0)	35.0 (18.0–236.0)**
>40	60 (23.5%)	44 (20.6%)	16 (39.0%)*
High-sensitivity C-reactive protein (mg/L)	30.8 (0.1–300.6)	22.1 (0.1–208.9)	97.9 (3.1–300.6)***
Lactate dehydrogenase (U/L)	291.0 (54.6–1196.0)	273.0 (54.6–715.0)	509.0 (213.0–1196.0)***
Creatinine (μmol/L)	68.0 (29.0–427.0)	67.0 (31.0–354.0)	80.0 (29.0–427.0)*
Fasting plasma glucose (mmol/L)	6.1 (3.9–23.1)	5.8 (3.9–18.9)	10.1 (4.8–23.1)***
≥7.0	86 (33.7%)	51 (23.8%)	35 (85.4%)***
≥11.1	30 (11.8%)	11 (5.1%)	19 (46.3%)***
$HbA1_C$ (%)	6.1 (4.9–12.5)	6.0 (4.9–12.5)	7.2 (5.1–11.6)***
Cardiac troponin (pg/mL)	5.3 (1.9–11,672)	3.9 (1.9–411.4)	21.1 (3.1–11,672)***
Creatine kinase-MB (ng/mL)	0.7 (0.1–18.6)	0.7 (0.1–8.1)	1.0 (0.2–18.6)**
Procalcitonin (ng/ml)	0.05 (0.02–4.1)	0.04 (0.02–1.3)	0.2 (0.02–4.1)***
IL-6 (pg/mL)	12.3 (1.5–374.4)	8.7 (1.5–304.7)	36.5 (2.4–374.4)***
IL-8 (pg/mL)	11.3 (5.0–338.0)	10.6 (5.0–338.0)	25.0 (5.0–268.0)***
IL-10 (pg/mL)	5.0 (5.0–62.9)	5.0 (5.0–38.6)	10.1 (5.0–62.9)***
TNF-α (pg/mL)	7.6 (4.0–69.7)	7.2 (4.0–42.2)	9.3 (4.0–69.7)**
Serum ferritin (μg/L)	648.4 (25.4–8,202.0)	530.7 (25.4–6981.0)	1396 (87.4–8,202.0)***

Compared to non-ICU patients *P < 0.05; **P < 0.01; ***P < 0.001.

The most common symptoms on admission were fever (88.6%) and cough (79.2%), and less common manifestations were shortness of breath (43.9%), diarrhea (22.7%), and muscle ache (18.8%). Approximately 50% of patients had comorbidities, with a predominance of hypertension (101, 39.6%), diabetes (51, 20.0%), and coronary heart disease (28, 10.9%) (Table 1).

There are no currently approved therapies or vaccines for COVID-19. In our cohort, 207 (81.2%) patients received antiviral drugs, including ribavirin, lopinavir/ritonavir tablets, arbidol hydrochloride, and chloroquine (Table 1).

3.2. *Clinical and laboratory findings in COVID-19 patients*

A total of 214 (83.9%) patients were admitted to isolation wards, 41 (16.1%) were admitted to ICUs because of organ dysfunction, and 30 (11.8%) died. Among ICU patients, eight (19.5%) used non-invasive mechanical ventilation, and 33 (80.5%) received invasive mechanical ventilation. Extracorporeal membrane oxygenation was required in three patients, of whom one survived.

Most ICU patients were men (71.8%). There were significant differences in laboratory findings between the two study groups (Table 2). ICU patients presented higher white blood cell and neutrophil counts and lower lymphocyte counts compared to non-ICU patients. Plasma prothrombin time, D-dimer, hs-CRP, creatine kinase, lactose dehydrogenase, IL-6, IL-8, IL-10, TNF-α, and ferritin were significantly higher in ICU patients ($p < 0.05$) (Table 1).

The prevalence of known diabetes was significantly higher in the ICU group (31.7% vs. 17.8%, $p = 0.0408$). FPG levels on admission were higher in ICU patients (median, 10.1 mmol/L [4.8–23.1]) than non-ICU patients (median, 5.8 mmol/L [3.9–18.9], $p < 0.001$). FPG levels ≥7 and ≥11.1 mmol/L were more predominant in ICU than non-ICU patients, respectively ($p < 0.001$) (Table 1).

A total of 27.1% (69/255) patients received corticosteroid therapy with methylprednisolone or prednisone. Compared with non-ICU patients, corticosteroids were prescribed more

Table 2 – Corticosteroid therapy in patients with COVID-19.

	Total (n = 69)	Non-ICU (n = 40)	ICU (n = 29)
Age (years)	66 (36–92)	66.00 (42–92)	65.50 (36–88)
Male (%)	35 (50.7%)	16 (40.0%)	19 (65.5%)*
Duration of illness (days)	11.00 (3–30)	11.00 (3–30)	12 (5–30)
Course of corticosteroid treatment (days)	6.5 (2–16)	6.0 (2–14)	6.5 (2–16)
Total corticosteroid dose (mg/day)	280.0 (80–1400)	230.0 (80–900)	450.0 (80–1400)*
Average daily dose (mg/day)	40.0 (16.4–160)	40.0 (20–80)	54.85 (16.4–160)*
Maximum dose (mg/day)	60.0 (20–320)	40.0 (20–160)	80.0 (40–320)**
History of diabetes (%)	20 (28.9%)	9 (22.5%)	11 (37.9%)
Insulin treatment (%)	28 (40.6%)	6 (15.0%)	22 (75.9%)***
Oral hypoglycemic agent	12 (17.4%)	8 (20.0%)	4 (13.8%)

Compared to non-ICU patients *P < 0.05; **P < 0.01; ***P < 0.001.

often to ICU patients (70.7% vs. 18.7%, p < 0.001). Steroid doses were converted to equivalent doses of methylprednisolone (e.g., 5 mg prednisone was converted to 4 mg methylprednisolone). The total dose, average daily dose, and maximum dose of corticosteroids were significantly higher in the ICU group (Table 2). During therapy, 35% (14/40) non-ICU patients received hypoglycemic treatment, including insulin (42.9%, 6/14) or oral hypoglycemic agents (57.1%, 8/14). In contrast, 89.7% (26/29) ICU patients received hypoglycemic treatment, including insulin (84.6%, 22/26) or oral hypoglycemic drugs (15.3%, 4/26). Insulin therapy was prescribed more often to ICU patients (Table 2). A total of 201 patients had complete data for FPG (160 non-ICU and 41 ICU patients). The changes in FPG levels are shown in Fig. 1. FPG levels were consistently higher in ICU patients irrespective of steroid treatment status. These levels tended to peak between days 4 and 13 days after admission and decreased to near-normal values between days 16 and 19 days (Fig. 1).

3.3. *Risk factors for poor outcomes in COVID-19*

Multivariable logistic regression analysis was used to assess the risk factors for poor outcomes (ICU admission or death). The analysis by age, sex, duration of illness, history of diabetes, FPG, D-dimer greater than 1 mg/mL, and IL-6 showed that a history of diabetes [odds ratio (OR), 0.099; 95% confidence interval (CI), 0.016–0.627; p = 0.014], higher FPG at admission (OR, 1.587; 95% CI, 1.299–1.939, p < 0.001), high IL-6 level (OR, 1.01; 95% CI, 1.002–1.018, p = 0.013), and D-dimer greater than 1 mg/L at admission (OR, 4.341; 95% CI, 1.139–16.547, p = 0.032) were independent predictors of ICU admission.

The probability of ICU admission among patients stratified by tertiles of FPG levels on admission was higher in the highest tertile (≥11.1 mmol/L) (Fig. 2). Cox proportional hazards analysis showed that, compared with FPG < 7 mmol/L, FPG levels of 7.0–11.1 mmol/L and ≥ 11.1 mmol/L were associated with an increased hazard ratio (HR) for ICU admission (HR, 5.538 [95% CI, 2.269–13.51] and 11.55 [4.45–29.99], respectively).

4. Discussion

Most COVID-19 patients have mild symptoms; however, approximately 15% cases progress to severe pneumonia and approximately 5% evolve to ARDS with or without multiple organ failure [6–7]. Yang et al. [8] have shown that the mortality rate in critically ill patients admitted to the ICU is 61.5%.

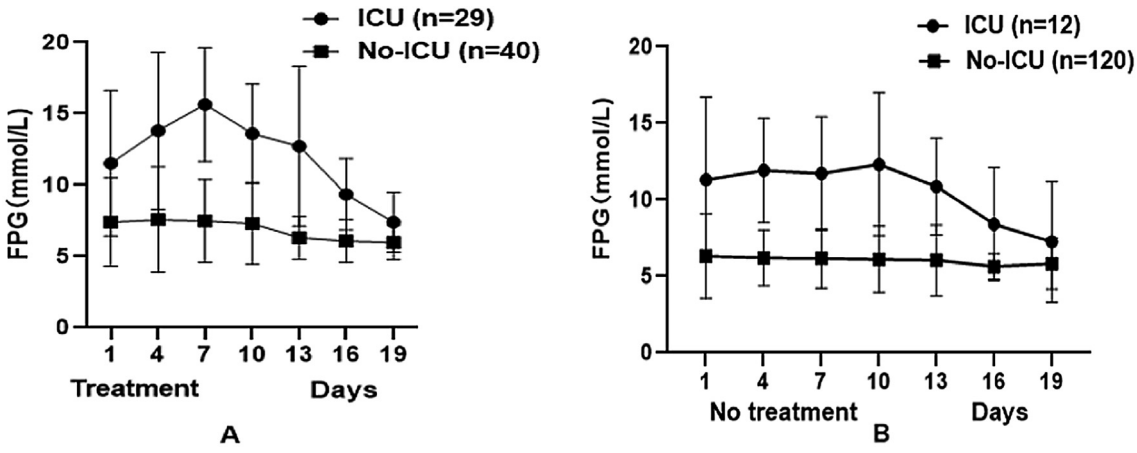

Fig. 1 – Changes in fasting plasma glucose (FPG) levels in hospitalized patients with COVID-19. A, treatment with corticosteroid; B, no treatment with corticosteroid. Differences between ICU and non-ICU patients were significant at all time points.

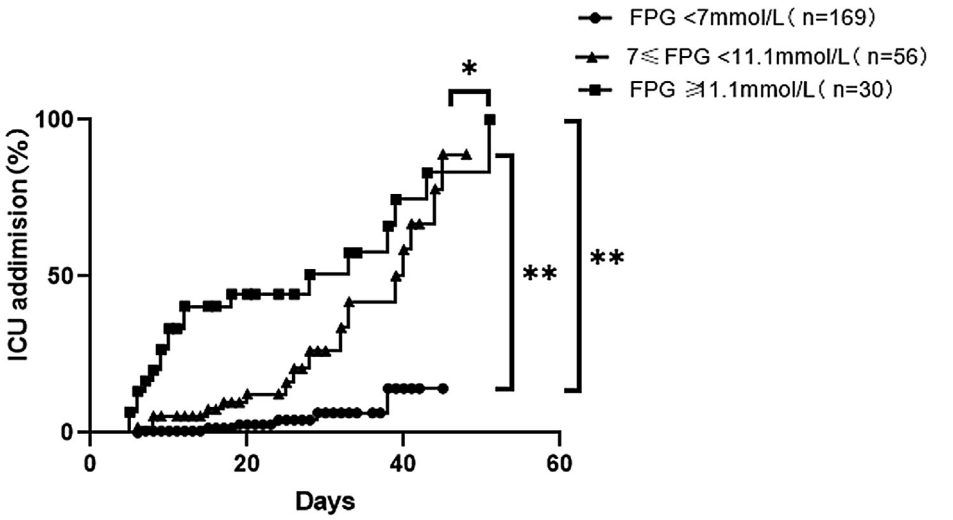

Fig. 2 – Probability of ICU admissions among COVID-19 patients stratified by tertiles of fasting plasma glucose (FPG) level on admission (<7.0, 7.0–11.0 mmol/L, and ≥ 11.0 mmol/L). *P < 0.05, **P < 0.001 (log-rank [Mantel-Cox] test).

Therefore, identifying prognostic biomarkers in high-risk patients and managing this patient group at an early stage is crucial. The risk factors for poor outcomes (ICU admission or death) were a history of diabetes, D-dimer levels higher than 1 mg/L, and high levels of FPG and IL-6 on admission. In addition, lymphopenia and increased levels of cardiac troponin I, serum ferritin, lactate dehydrogenase, and hs-CRP were more common in ICU patients, which agrees with previous studies [6–8,19].

Twenty percent of our cohort had a known history of diabetes, and ICU patients were more likely to have underlying diabetes compared with non-ICU patients. It has been shown that diabetes increases the risk of death from SARS and MERS [13,20]. Yang et al. [13] observed that, among SARS patients, the rate of diabetes was significantly higher in non-survivors than survivors (21.5% vs. 3.9%). Badawi et al. [20] showed that the overall prevalence of diabetes in MERS patients was 54.4%, and the OR of severe disease or death from MERS in diabetics ranged from 2.47 to 7.24. Understanding the factors associated with poor outcomes in diabetes may improve the clinical management of severe cases. It was shown that influenza virus infection and proliferation were significantly enhanced in pulmonary epithelial cells exposed to high glucose concentrations in vitro. Kirsten et al. [12] found that MERS-CoV infection impaired the antiviral immune response in diabetic mice, resulting in more severe pathology in the lungs. Notwithstanding, further experimental studies are necessary to determine the role of diabetes in the pathogenesis and prognosis of viral respiratory diseases.

The FPG levels were consistently higher in ICU patients than non-ICU patients irrespective of corticosteroid status. After adjusting for age, gender, and disease duration, FPG levels at admission were an independent predictor of poor prognosis in COVID-19 (OR, 1.587). Moreover, Cox proportional hazards analysis showed that elevated FPG (7.0–11.0 and ≥11.0 mmol/L) was associated with an increased HR of poor clinical outcomes (5.538 and 11.55, respectively), suggesting that hyperglycemia might predict the severity of viral infections with multisystem involvement and augment the severity of COVID-19. Several viruses, including Coxsackie B, rubella, mumps, cytomegalovirus, and varicella-zoster, have been associated with the development of primary type 1 diabetes [21–22]. Yang et al. [13] found that FPG levels were higher in patients with mild SARS not receiving glucocorticoid therapy than in patients with non-SARS viral pneumonia. Structural analysis suggests that SARS-CoV-2 can bind to human angiotensin-converting enzyme 2 (ACE2) receptors, as occurs with SARS-CoV [3–4]. An immunostaining study [23] found that ACE2 was highly expressed in lung, kidney, heart, and endocrine pancreatic islets and poorly expressed in exocrine pancreatic tissues. These results suggest that SARS-CoV-2 invades pancreatic islets through ACE2 receptors and causes disease by triggering acute hyperglycemia. Nonetheless, more studies are required to confirm this hypothesis.

The use of steroids in patients with COVID-19 remains controversial. Several studies argue against this therapy in COVID-19 [24], and physicians prefer using corticosteroids in severe patients [25]. The pathological features of COVID-19 include excessive inflammation and cytokine-related lung injury, which underscores the need for the timely and appropriate use of corticosteroids in severe patients to prevent ARDS [26–27]. A retrospective study of 401 patients with SARS has shown that the proper use of corticosteroids decreased mortality and the length of hospital stay in critical ill SARS patients without increasing the risk of secondary lower respiratory tract infections and other complications [28]. The Chinese Thoracic Society recommends interventions with short courses of low to moderate-dose corticosteroids in critically ill patients with COVID-19 [29]. Steroid therapy increases the risk of hyperglycemia. Xiao et al. [30] reported that among 95 SARS patients given over-dose steroid therapy, 34.7% developed steroid-induced diabetes, and the daily maximum dose of methylprednisolone was the only predictor of diabetes. Low to moderate doses of steroids were administered to

27.1% patients with COVID-19 in our cohort. During steroid therapy, 35% of non-ICU patients and 89.7% of ICU patients were given insulin or an oral hypoglycemic drug, respectively; however, the FPG of most patients returned to near-normal values after therapy. Steroid treatment has advantages and disadvantages; therefore, the use of proper doses, close glucose monitoring, and timely normalization of blood glucose levels are essential during treatment.

Our study has some limitations. First, the study used a single-center, retrospective, and observational design. Second, sample size was relatively small. Third, most patients with COVID-19 were seriously ill and came from hospitals assigned by the government, potentially leading to selection bias.

In our cohort, a known history of diabetes and high FPG levels on admission predicted poor prognosis. Intensive surveillance and insulin therapy are crucial to regulate metabolic homeostasis and improve clinical outcomes in COVID-19 patients, in view of the potentially detrimental effects of hyperglycemia on organ function.

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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