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A Retrospective Study of 268 Patients with SARS-CoV-2 Infection to Evaluate the Association Between Blood Glucose and Severity of COVID-19 Pneumonia and Patient Mortality

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Background: Diabetes is one of the most commonly reported comorbidities among patients infected with SARS-CoV-2. This retrospective study of patients with SARS-CoV-2 infection was conducted to evaluate the association between blood glucose levels and the severity of COVID-19 pneumonia and patient mortality.

Material/Methods: A total of 268 patients with confirmed SARS-CoV-2 infection were included in this retrospective study. We obtained demographic characteristics, clinical symptoms, laboratory data, and survival information from patients' electronic medical records. Blood glucose was measured on admission to the hospital. Comorbidities, including hypertension, diabetes, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and cardiovascular disease, were collected by self-reported medical history.

Results: Significantly higher risks of severe COVID-19 were found in patients with blood glucose levels ranging from 5.53 to 7.27 mmol/L (odds ratio [OR], 3.98; 95% confidence interval [CI], 1.81-8.75) and in patients with blood glucose ≥7.27 mmol/L (OR, 12.10; 95% CI, 5.53-26.48) than in those with blood glucose <5.53 mmol/L. There was a trend toward better survival in patients with blood glucose <5.53 mmol/L than in patients with blood glucose from 5.53 to 7.27 mmol/L (hazard ratio [HR], 6.34; 95% CI, 1.45-27.71) and ≥7.27 mmol/L (HR, 19.37; 95% CI, 4.68-80.17). Estimated 10-day overall survival rates were 96.8%, 90.6%, and 69.3% in patients with blood glucose <5.53 mmol/L, 5.53 to 7.27 mmol/L, and ≥7.27 mmol/L, respectively.

Conclusions: Hyperglycemia was association with severity of COVID-19 pneumonia and with increased patient mortality. These findings support the need for blood glucose monitoring and control of hyperglycemia in patients with COVID-19 pneumonia.

Keywords: Blood Glucose • COVID-19 • Hyperglycemia • Severe Acute Respiratory Syndrome Coronavirus 2 • Survival Analysis

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Background

In December 2019, COVID-19 occurred in Wuhan, Hubei Province, China. Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has been regarded as the pathogen causing COVID-19 disease, which mainly invades the respiratory tract and lungs [1]. Severe COVID-19 disease can rapidly trigger acute, even lethal, lung failure [2].

Diabetes is a major cause of mortality worldwide. The association between infection and diabetes has long been demonstrated, and patients with diabetes have a poorer progression and prognosis once infected than those without diabetes [3]. Diabetes and uncontrolled blood glucose levels can affect mortality in cases of SARS-CoV infection [4]. In addition, patients with diabetes are more likely to be infected with other bacteria and viruses, including *Staphylococcus aureus* [5], *Mycobacterium tuberculosis* [6], and MERS-CoV [7]. Diabetes is one of the most commonly reported comorbidities among patients infected SARS-CoV-2. Reports have shown that 22.2% to 26.9% of patients with severe COVID-19 have type 2 diabetes [2,8,9]. Hyperglycemia can reduce the mobilization of leukocytes and decrease phagocytic activity. Hyperglycemia can impair pulmonary endothelial function and reduce antioxidant levels. The increase of glucose levels in the lungs is related to high lung pathogen growth and reduced intracellular bactericidal activity [10]. When patients with COVID-19 are known to have a medical history of diabetes, doctors will control blood glucose throughout treatment. Rather than focusing on the relationship between diabetes and COVID-19, we focused on the relationship between blood glucose levels and COVID-19 to avoid the impact of treatment.

Therefore, this retrospective study of patients with SARS-CoV-2 infection was conducted to evaluate the association between blood glucose levels and the severity of COVID-19 pneumonia and patient mortality.

Material and Methods

Study Population

A total of 268 patients with confirmed COVID-19 were treated at Tongji Hospital from February 2 to March 25, 2020, in this retrospective study. All patients met the inclusion criteria: (1) epidemiology history, (2) positive result for SARS-Cov-2 RNA by real-time polymerase chain reaction (PCR) or positive results of SARS-CoV-2 IgM and IgG antibodies in serum specimens, and (3) chest computed tomography (CT) finding abnormalities indicative of viral pneumonia. Patients were excluded when there was missing data on blood glucose levels or on the severity of COVID-19 disease. SARS-CoV-2 was examined by real-time reverse transcription PCR (RT-PCR) assay. The real-time RT-PCR assay was performed using a 2019-nCoV nucleic acid detection kit, according to the manufacturer's protocol (Sichuan Maccura Biotech Co., Ltd., China). Recorded information included demographic data, clinical symptoms, laboratory data, and survival information from patients' electronic medical records. The Ethics Committee of Tongji Hospital (Wuhan, China) and China-Japan Union Hospital of Jilin University approved this study.

Definitions

The hexokinase method was used to measure fasting blood glucose levels, which were measured after overnight fasting and before breakfast. The standard reference range was 3.9 to 6.1 mmol/L. Comorbidities, including hypertension, diabetes, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and cardiovascular disease, were based on the patients' self-reported medical history. Patients were divided into a severe COVID-19 group and a nonsevere COVID-19 group. Classification of severe COVID-19 required at least 1 of the following criteria: (1) respiratory rate ≥30/min, (2) finger oxygen saturation ≤93% in a resting state, (3) arterial oxygen tension/inspiratory oxygen fraction ≤300 mmHg, and (4) clinical symptoms that were gradually aggravated, with lung imaging showed that the lesions progressed >50% within 24 to 48 h [11]. Survival time was the time between admission and discharge from the hospital or death. The primary outcome was defined as the in-hospital mortality of patients with COVID-19.

Statistical Analysis

The differences in baseline characteristics between the groups were measured using the Pearson chi-squared test or Fisher's exact test for categorical variables and the *t* test or Mann-Whitney U test for continuous variables, as appropriate. Odds ratios (OR) of severe COVID-19 were estimated by modeling blood glucose as a categorical variable using logistic regression. Survival rates were calculated using the Kaplan-Meier method, and the log-rank test was performed to assess the differences between groups. We performed multivariate Cox regression analysis to identify the factors independently related to prognosis. All data were analyzed using IBM SPSS version 24.0. Results with $P<0.05$ (2-tailed) were considered statistically significant.

Results

Baseline Characteristics of Patients

A total of 268 patients with COVID-19 were included in this retrospective study. Among these patients, 96 patients had severe COVID-19, and 172 patients had nonsevere COVID-19. The patients' baseline characteristics are shown in **Table 1**.

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Table 1. The baseline characteristics of patients with COVID-19 (n, interquartile range, or percentage).

Characteristics	Total (n=268)	Severe (n=96)	Non-severe (n=172)	P
Age, years	57.75 (67.00, 73.00)	70.00 (64.00, 76.75)	65.00 (54.00, 72.00)	<0.001
Sex				0.036
Male	139 (51.9)	58 (60.4)	81 (47.1)	
Female	129 (48.1)	38 (39.6)	91 (52.9)	
Comorbidities				
Hypertension	43/109 (39.4)	27/69 (39.1)	16/40 (40.0)	0.929
Diabetes	21/109 (19.3)	17/69 (24.6)	4/40 (10.0)	0.062
Cardiovascular disease	12/109 (11.0)	8/69 (11.6)	4/40 (10.0)	1.000
Chronic kidney disease	1/109 (0.9)	1/69 (1.4)	0/40 (0.0)	1.000*
Chronic liver disease	1/109 (0.9)	1/69 (1.4)	0/40 (0.0)	1.000*
Chronic obstructive pulmonary disease	3/109 (2.8)	2/69 (2.9)	1/40 (2.5)	1.000*
Blood glucose, mmol/L	6.20 (5.28, 8.14)	7.42 (6.02, 10.55)	5.72 (5.12, 6.89)	<0.001
Leukocyte count, $\times 10^9$/L	6.17 (4.80, 8.99)	9.26 (6.03, 12.35)	5.64 (4.53, 6.98)	<0.001
Neutrophil count, $\times 10^9$/L	4.37 (3.13, 7.42)	7.94 (4.55, 11.91)	3.81 (2.61, 4.78)	<0.001
Lymphocyte count, $\times 10^9$/L	0.97 (0.65, 1.42)	0.64 (0.45, 0.89)	1.22 (0.85, 1.60)	<0.001
ALT, U/L	24.50 (16.00, 41.00)	29.00 (19.00, 42.75)	23.00 (14.00, 40.00)	0.021
AST, U/L	27.00 (19.00, 45.00)	41.00 (25.25, 62.00)	23.50 (18.00, 34.00)	<0.001
LDH, U/L	290.00 (225.25, 455.00)	480.00 (333.25, 635.50)	252.50 (209.75, 328.75)	<0.001
Total bilirubin, μmol/L	10.50 (7.30, 14.60)	13.10 (9.53, 18.20)	9.50 (7.00, 13.00)	<0.001
Creatinine, μmol/L	74.50 (60.25, 92.75)	85.50 (68.25, 109.75)	70.00 (59.00, 84.00)	<0.001
Duration of hospitalization, days	20.00 (9.25, 27.00)	16.00 (5.25, 28.00)	21.00 (12.25, 27.00)	0.058

ALT – alanine aminotransferase; AST – aspartate transaminase; LDH – lactic dehydrogenase

The median age of all patients was 58 years (range 20-88 years; interquartile range, 67-73 years), and 51.9% were men. Patients with severe COVID-19 were older than those with non-severe COVID-19 (70 years vs 65 years) and had a higher percentage of men (60.4% vs 47.1%). We had comorbidity data for only 109 patients, with 61 of 109 patients having a history of comorbidities. In the severe COVID-19 group, 38 patients had comorbidities, and 23 patients had comorbidities in the nonsevere COVID-19 group; no significant differences were found in comorbidities between the 2 groups ($P>0.05$). Patients with severe COVID-19 also had higher neutrophil and leukocyte counts and higher blood glucose, aspartate transaminase (AST), alanine transaminase, lactate dehydrogenase (LDH), total bilirubin, and creatinine levels and lower lymphocyte counts than patients with nonsevere COVID-19 ($P<0.05$). We did not observe a significant difference in duration of hospitalization between the 2 groups.

Association Between Blood Glucose and Severe COVID-19

When blood glucose was assessed by tertiles, significantly higher risks of severe COVID-19 were found in patients with blood glucose levels ranging from 5.53 to 7.27 mmol/L (OR, 3.98; 95% CI, 1.81-8.75) and in patients with blood glucose levels ≥7.27 mmol/L (OR, 12.10; 95% CI, 5.53-26.48) than in patients with blood glucose levels <5.53 mmol/L. After adjusting for sex and age by logistic regression, the ORs were 3.43 (95% CI, 1.53-7.70) and 8.82 (95% CI, 3.92-19.83), respectively (**Table 2**).

Survival Analysis of Patients with COVID-19

The survival curve of patients with COVID-19 is shown in **Figure 1**. This curve showed a trend toward better overall survival (OS) in patients with blood glucose levels of <5.53 mmol/L than in patients with blood glucose levels ranging from 5.53 to

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Table 2. Relationship of blood glucose with the risk of severe COVID-19.

FPG	Severe/non-severe	Unadjusted			Adjusted*		
		OR (95% CI)		*P*	OR (95% CI)		*P*
Q1	10/77	Ref			Ref		
Q2	31/60	3.98	(1.81-8.75)	0.001	3.43	(1.53-7.70)	0.003
Q3	55/35	12.10	(5.53-26.48)	<0.001	8.82	(3.92-19.83)	<0.001

* Adjusted for age and sex. Q1, <5.53 mmol/L; Q2, 5.53-7.27 mmol/L; Q3, ≥7.27 mmol/L.

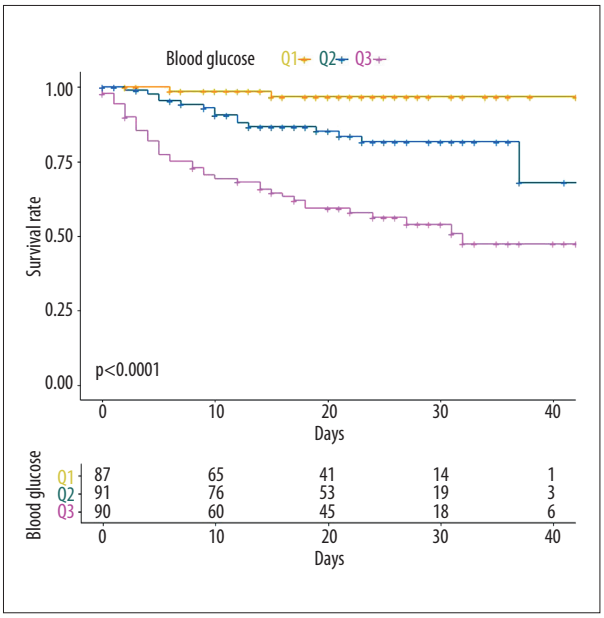

Figure 1. Survival curve of patients with COVID-19 divided by tertiles of blood glucose levels on admission. Q1, <5.53 mmol/L; Q2, 5.53-7.27 mmol/L; Q3, ≥7.27 mmol/L.

7.27 mmol/L (hazard ratio [HR], 6.34; 95% CI, 1.45-27.71) and ≥7.27 mmol/L (HR, 19.37; 95% CI, 4.68-80.17). The estimated 10-day OS rates were 96.8%, 90.6%, and 69.3% in patients with blood glucose levels of <5.53 mmol/L, 5.53 to 7.27 mmol/L, and ≥7.27 mmol/L, respectively. Patients with blood glucose <5.53 mmol/L and patients with blood glucose levels ranging from 5.53 to 7.27 mmol/L did not reach the median survival time. The median survival duration was 32 days in patients with blood glucose levels of ≥7.27 mmol/L. The univariate log-rank test showed that several covariates were significantly associated with OS, including leukocyte, neutrophil, and lymphocyte counts and blood glucose, AST, LDH, total bilirubin, and creatinine levels ($P<0.05$). In multivariate Cox regression analysis, patients with blood glucose levels of ≥7.27 mmol/L had poorer OS than those with blood glucose levels of <5.53 mmol/L (HR, 10.13; 95% CI, 2.37-43.31). However, there was no difference in OS between patients with blood glucose levels of <5.53 mmol/L and patients with blood glucose levels ranging from 5.53 to 7.27 mmol/L (HR, 4.22; 95% CI, 0.94-19.01) (**Table 3**).

Discussion

Diabetes is one of the leading comorbidities association with the severity of 3 coronavirus infections, including MERS-CoV, SARS-CoV, and SARS-CoV-2. A previous study showed that compared with patients without diabetes, patients with diabetes have a 50% higher risk of death from COVID-19 [12]. In this retrospective study of SARS-CoV-2 infection, we found a positive association between blood glucose levels and the risk of severe COVID-19. A similar trend was found in survival analysis. Patients in the highest tertile of blood glucose levels had the lowest survival rates. In other words, the higher the blood glucose level, the greater the risk of severe disease or death.

The significant laboratory findings were elevated leukocyte and neutrophil counts and low lymphocyte counts in patients with severe COVID-19, compared with those with nonsevere COVID-19. One study observed that patients with COVID-19 have markedly low lymphocyte counts [13]. Poorly controlled diabetes is related to the inhibition of the lymphocyte proliferative response to different stimuli, release of interleukin 10, and the reduction in the fluidity, chemotaxis, and phagocytosis of polymorphonuclear leukocytes. With the increase of glycosylated hemoglobin A1c, the glycosylation degree of immunoglobulin in patients with diabetes increases, which directly damages the biological function of antibodies. When patients were grouped according to whether they had diabetes or not, several studies revealed that the lymphocyte counts of patients with diabetes are remarkably lower than those without diabetes, while leukocyte and neutrophil counts are higher [14,15]. In multivariate Cox regression analysis, we found neutrophils and lymphocytes were independent prognostic factors for mortality in patients with COVID-19.

A study conducted by Zhu et al showed that all-cause mortality in patients with COVID-19 with well-controlled blood glucose levels was significantly lower than that of those with poorly controlled blood glucose [16]; this is consistent with our study. Diabetes can be further aggravated after viral infection. Diabetes combined with SARS-CoV-2 infection can cause higher stress conditions and release more hyperglycemic hormones, leading to a dramatic fluctuation of blood glucose levels and abnormal

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Table 3. Univariate and multivariate survival analysis of overall survival in patients with COVID-19.

Characteristics	Univariate analysis		Multivariate analysis		
	Log-rank χ^2	P	HR	95% CI	P
Age, years	0.938	0.333			
<60			Ref		
≥60			1.129	0.538-2.368	0.748
Sex	2.914	0.088			
Female			Ref		
Male			0.735	0.406-1.330	0.309
Blood glucose, mmol/L	41.608	<0.001			
Q1			Ref		
Q2			4.221	0.937-19.012	0.061
Q3			10.128	2.368-43.306	0.002
Leukocyte count, $\times 10^9$/L	38.606	<0.001			
Normal			Ref		
Unnormal			1.283	0.624-2.638	0.498
Neutrophil count, $\times 10^9$/L	52.032	<0.001			
Normal			Ref		
Unnormal			3.456	1.553-7.689	0.002
Lymphocyte count, $\times 10^9$/L	27.903	<0.001			
Normal			Ref		
Unnormal			4.579	1.360-15.416	0.014
ALT, U/L	0.488	0.485			
Normal			Ref		
Unnormal			0.870	0.464-1.632	0.665
AST, U/L	21.184	<0.001			
Normal			Ref		
Unnormal			1.656	0.863-3.176	0.129
LDH, U/L	10.629	0.001			
Normal			Ref		
Unnormal			2.031	0.256-16.088	0.502
Total bilirubin, μmol/L	14.550	<0.001			
Normal			Ref		
Unnormal			2.687	1.075-6.716	0.035
Creatinine, μmol/L	6.585	0.010			
Normal			Ref		
Unnormal			1.454	0.820-2.579	0.200

Q1, <5.53 mmol/L; Q2, 5.53-7.27 mmol/L; Q3, ≥7.27 mmol/L. ALT – alanine aminotransferase; AST – aspartate transaminase; LDH – lactic dehydrogenase.

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blood glucose variability [17]. SARS-CoV and SARS-CoV-2 invade cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptors of host cells [18]. The ACE2 protein is widely expressed in the human body, including in the heart and respiratory tract [19]. A study showed that immunostaining of ACE2 was stronger in islets than in exocrine tissues, suggesting that ACE2 protein is present in islet B cells and SARS-Cov-2 may cause hyperglycemia by damaging islets [20]. Therefore, COVID-19 cases with hyperglycemia have worse outcomes. The more severe cases of COVID-19 were in men in the present study. The expression of ACE2 protein in men was almost 3 times higher than that in women [14], which may be the reason men are more susceptible to severe COVID-19.

It is very important to monitor blood glucose levels and strengthen blood glucose control to reduce the severity of disease and mortality in patients with diabetes and SARS-CoV-2 infection. The results of our study showed that patients with blood glucose levels of <5.53 mmol/L had the lowest risk of severe disease and mortality. However, this does not mean that the lower the blood sugar, the better the outcome. Hypoglycemia can mobilize proinflammatory monocytes and increase the reactivity of platelets, leading to higher cardiovascular mortality in patients with diabetes.

Zhu et al found that maintaining glycemic variability between 3.9 mmol/L and 10.0 mmol/L is associated with reduced adverse outcomes and mortality [16].

There are several limitations in our study. First, the history of comorbidities of some patients with COVID-19 was not obtained owing to the difficulty of data collection; therefore, we did not include the history of comorbidities in the univariate and multivariate survival analysis. Second, this retrospective study has a small sample size, so the conclusions should be extended to other populations with caution.

Conclusions

The findings from this retrospective study showed that hyperglycemia was association with the severity of COVID-19 pneumonia and increased patient mortality. These findings support the need for blood glucose monitoring and control of hyperglycemia in patients with COVID-19 pneumonia.

Conflicts of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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