Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
J-shaped association between fasting blood glucose levels and COVID-19 severity in patients without diabetes

Bing Zhu a,1, Shengwei Jin b,1, Lianpeng Wu c, Chenchan Hu c, Zhen Wang d, Le Bu a, Hang Sun a, Xingchun Wang a, Shen Qu a,*, Dong Chen c,*

a Department of Endocrinology and Metabolism, Shanghai Tenth People’s Hospital, School of Medicine, Tongji University, Shanghai, China
b Department of Anaesthesia and Critical Care, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Zhejiang, China
c Departments of Infectious Disease, The Ding Li Clinical College of Wenzhou Medical University and Sixth People’s Hospital of Wenzhou, Wenzhou, Zhejiang, China
d Zhejiang Provincial People’s Hospital, People’s Hospital of Hangzhou Medical College, Hangzhou, China

ARTICLE INFO

Article history:
Received 25 June 2020
Received in revised form 31 July 2020
Accepted 18 August 2020
Available online 25 August 2020

Keywords:
Coronavirus disease 2019 (COVID-19)
Hyperglycemia
Hypoglycemia
Fasting blood glucose
Glycemic target

ABSTRACT

Aims: Coronavirus disease 2019 (COVID-19) has become a recognized worldwide pandemic. Researchers now know that mortality from COVID-19 can be reduced through early prevention measures. This retrospective, multi-centered study of 293 COVID-19 patients without diabetes explores the association between fasting blood glucose (FBG) levels and the risk of COVID-19 disease progression, with the goal of providing clinical evidence for glycemic targets in patients.

Methods: The multivariate stepwise binary logistic regression analysis was used to test the dose–response effects of FBG levels on the risk of severe and critical condition in COVID-19 patients.

Results: FBG levels were plotted in quintiles with set at <4.74, 4.74–5.21, 5.21–5.78, 5.78–7.05, and ≥7.05 mmol/L. The constituent ratio of severe or critical cases in each FBG quintile was 20.7%, 1.7%, 13.8%, 27.1%, and 67.2%, respectively (P < 0.0001). When the second quintile was used as the reference, the adjusted odds ratios (AORs) (95%CI) for the risk of severe/critical condition in COVID-19 was 25.33 (2.77, 231.64), 1.00 (Reference), 3.13 (0.33, 29.67), 10.59 (1.23, 91.24), 38.93 (4.36, 347.48) per FBG quintile respectively (P < 0.001).

Conclusions: We provide evidence of J-shaped associations between FBG and risk of severe and critical condition in non-diabetes patients with COVID-19, with nadir at 4.74–5.78 mmol/L.
1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is becoming a pandemic worldwide. By the middle of June 2020, the disease has reached 216 countries, areas or territories, with over 8.24 million cases of infection and over 445 thousand confirmed deaths (WHO, https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Generally, many patients who had severe infection progressed rapidly to critical condition including multi-organ failure and sometimes death [1]. Better early warning signs of probable rapid progression of COVID-19 could help doctors anticipate and more rapidly act to prevent escalation in patients with severe symptoms of COVID-19.

Researchers are beginning to reach a consensus that COVID-19 patients with hyperglycemia or diabetes are associated with a higher risk of severely ill and mortality [2–7]. Wang and his colleagues have reported that COVID-19 patients with hyperglycemia or diabetes are more likely to need ICU care [8]. Wang et al. also demonstrated that fasting blood glucose (FBG) ≥ 7 mmol/L at admission was an independent risk factor for 28-day mortality in COVID-19 patients without pre-existing diabetes [7]. These studies suggest that early management of blood glucose levels in COVID-19 may serve as a useful tool in managing the disease and saving lives. Interestingly, we noticed that Zhang et al. reported an appropriately 1% confirmed patients with COVID-19 presenting decreased glucose (<3.9 mmol/L) [9] suggesting that hyperglycemia may not be the exclusive relationship between blood glucose and COVID-19. The American Diabetes Association (ADA)’s criteria notes that hypoglycemia is generally defined as a blood glucose level <3.9 mmol/L (70 mg/dL) and that for nondiabetic individuals <2.8 mmol/L (50 mg/dL) is threshold for impairment of cognitive function [10,11], levels associated with a range of adverse clinical outcomes including death [10,12]. Studies have supported that both low and high levels of glycemic control have been associated with an increased mortality risk in diabetes patients [13]. However, few studies have looked at lower limit of blood glucose control other than hyperglycemia in COVID-19 patients without pre-existing diabetes. Current research does not provide sufficient evidence for doctors to judge the potential value of knowing an optimal glycemic target as a diagnostic tool in treating severe COVID-19 patients who do not have pre-existing diabetes.

The purpose of this study was to explore the association between fasting blood glucose (FBG) levels and risk of COVID-19 progressing into severe or critical condition in patients without pre-existing diabetes, thus providing clinical evidence for determining optimal glycemic targets.

2. Materials and methods

2.1. Subjects

This retrospective, multi-centered study drew data from five hospitals in Wenzhou, China. Records from 345 COVID-19 patients were initially included in the study, but 52 were excluded including children and adolescents, as well as patients with cancer, cachexia or pre-existing diabetes (Fig. 1). This left 293 patients records for the analysis, including 217 mild and moderate cases and 76 severe and critical cases. No one with end-stage chronic kidney disease, hepatic failure, hepatitis B, pancreatitis, hematological system diseases, cachexia, severe debilitating illness, and schizophrenia (Fig. 1).

2.2. Ethical statements

The study was approved by the Research Ethics Review Committee of Tongji University and Department of Infectious Diseases, Wenzhou Central Hospital and Sixth People’s Hospital of Wenzhou, Wenzhou, Zhejiang, China (No. K2020-01-005).
The diagnosis and classification criteria for COVID-19 in this study were based on guidelines from the Diagnosis and Treatment Program of New Coronavirus Pneumonia (seventh trial version, China) (http://www.nhc.gov.cn/). We confirmed SARS-CoV-2 infection by RT-PCR of samples taken from upper nasopharyngeal swabs. Two sets of primers were used for two target genes according to the protocol issued by the National Institute for Viral Disease Control and Prevention in China as previously described. [15]. The classification of severity included: (1) Mild, with mild symptoms, no pneumonia in imaging diagnosis, (2) Moderate, with fever, respiratory tract symptoms, and pneumonia in imaging diagnosis, (3) Severe, meeting criteria of either anhilation (respiratory rate ≥30 beats/min), or finger oxygen saturation (≤93% at resting, or arterial blood oxygen partial pressure at (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa), (4) Critical, where patients had either respiratory failure requiring mechanical ventilation, shock, or required ICU care for organ failure. We classified mild and moderate patients as the milder category, otherwise severe and critical ill patients as the severer category.

2.5. Statistical methods

Continuous data were presented as medians (interquartile ranges, IQR) or means ± standard deviations (SD) based on the data distribution. Categorical variables were presented as percentages (%). Student’s t-test or Mann-Whitney U test were used to compare continuous data between groups based on the homogeneity of variance test. Chi-squared (χ²) tests were used to compare categorical data between the groups. Z-tests (p-value adjusted by a Bonferroni method for multiple testing) were used to pairwise comparison. Spearman’s bivariate simple correlation analysis was conducted to explore the associations between FBG level and variables that demonstrated significant associations with the COVID-19 severity in the univariate binary logistic regression analysis. We excluded variables with 10% missing values. The multiple potential confounders were used as independent variables in the multivariate step-wise binary logistic regression analysis to test the combined effect of these factors on the adjusted odds ratios (AORs) for severe or critical condition in COVID-19. Each continuous variable was converted into a categorical variable before entered into models. All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and Graphpad prism 8.0 software. Results were considered to be statistically significant at two-tailed P value of <0.05.

3. Results

3.1. Patient characteristics

COVID-19 patients in this study were mostly mid-aged men. Most patients with mild and moderate symptoms had low grade fever, while patients classified as severe and critical had a medium or high body temperature. In comparison to mild and moderate cases, severe and critical patients had significantly higher FBG (5.30, IQR 4.80–5.90 vs. 7.35, IQR 5.60–9.58 mmol/L, P < 0.0001), BMI, C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GTT), and triglycerides (TG) levels. Conversely, COVID-19 patients in severe or critical condition had significantly lower HDL levels (1.15, IQR 0.97–1.41 vs. 1.02, IQR 0.83–1.25 mmol/L, P < 0.0001) (Table 1).

3.2. The severe and critical rate across FBG quintiles

FBG levels were plotted in quintiles with levels set at less than 4.74 mmol/L, 4.74–5.21 mmol/L, 5.21–5.78 mmol/L, 5.78–7.05 mmol/L, and greater than or equal to 7.05 mmol/L. The median value for each quintile was 4.50, 5.02, 5.50, 6.21, and 9.05 mmol/L, respectively. In the χ² tests, the expected frequency in each cell was greater than 5 and the minimum was 14.8. These results suggest that the sample size and cell distribution fully met χ² test’s requirements. As shown in Fig. 2, associations between FBG levels and the risk of severe and critical condition were non-linear for COVID-19 patients. The constituent ratio of severe and critical cases in each FBG
Table 1 – Characteristics of COVID-19 patients in this study.

| Characteristics                        | ALL (N = 293) | Mild and Moderate (N = 217) | Severe and Critical (N = 76) | P-Value |
|----------------------------------------|---------------|-----------------------------|-----------------------------|---------|
| Age (years)                            | 47.0(37.0, 55.5) | 44.0(34.0, 53.0) | 54.0(46.5, 66.75) | <0.0001 |
| Gender (male%)                         | 151(51.5%) | 107(49.3%) | 44(57.9%) | 0.197 |
| BMI (kg/m²)                            | 23.80 ± 3.39 | 23.43 ± 3.13 | 25.11 ± 3.91 | 0.001 |
| Body temperature (°C)                  | 37.70(37.0, 38.40) | 37.60(37.0, 38.0) | 38.40(37.58, 38.85) | <0.0001 |
| FBG (mmol/L)                           | 5.50(4.88, 6.60) | 5.30(4.80, 5.90) | 7.35(5.60, 9.58) | <0.0001 |
| FBG quintile (median)                  |               |               |               | <0.0001 |
| <4.74 (4.50 mmol/L)                    | 58(100%) | 46(79.3%) | 12(20.7%) | a* |
| 4.74–5.21 (5.02 mmol/L)                | 60(100%) | 59(98.3%) | 1(1.7%) | b |
| 5.21–5.78 (5.50 mmol/L)                | 58(100%) | 50(86.2%) | 8(13.8%) | a, b |
| 5.78–7.05 (6.21 mmol/L)                | 59(100%) | 43(72.9%) | 16(27.1%) | a |
| >7.05 (9.05 mmol/L)                    | 58(100%) | 19(32.8%) | 39(67.2%) | c |
| C-reactive protein (mg/L)              | 9.30(2.28, 24.13) | 7.90(2.30, 20.68) | 24.10(1.25, 44.93) | 0.048 |
| Creatine kinase (U/L)                  | 71.00(47.00, 105.0) | 71.80(46.50, 105.0) | 69.65(55.00, 104.0) | 0.746 |
| Lactate dehydrogenase (U/L)            | 210.5(174.0, 274.0) | 198.0(165.50, 241.75) | 272.0(208.0, 389.25) | <0.0001 |
| Lymphocyte count (× 10⁹/L)             | 1.20(0.90, 1.70) | 1.30(0.90, 1.70) | 1.0(0.78, 1.50) | 0.226 |
| Creatinine (µmol/L)                    | 62.0(55.25, 73.0) | 63.0(56.0, 75.0) | 62.0(55.0, 71.25) | 0.816 |
| Alanine aminotransferase (U/L)         | 22.0(15.0, 35.0) | 22.0(13.0, 33.0) | 24.0(17.25, 41.75) | 0.130 |
| Aspartate aminotransferase (U/L)       | 25.0(20.0, 35.0) | 23.0(18.0, 32.0) | 30.0(23.0, 43.0) | <0.0001 |
| Alkaline phosphatase (U/L)             | 55.0(42.25, 68.0) | 55.0(45.0, 68.0) | 52.0(34.75, 79.0) | 0.367 |
| Gamma-glutamyl transpeptidase (U/L)    | 22.5(15.0, 47.50) | 21.0(15.0, 42.0) | 43.5(19.25, 91.0) | 0.007 |
| Cholesterol (mmol/L)                   | 3.97 ± 0.86 | 3.95 ± 0.86 | 4.02 ± 0.87 | 0.563 |
| Triglycerides (mmol/L)                 | 1.17(0.91, 1.62) | 1.11(0.88, 1.58) | 1.40(1.01, 1.69) | 0.006 |
| High density lipoprotein(mmol/L)       | 1.10(0.93, 1.33) | 1.15(0.97, 1.41) | 1.02(0.83, 1.25) | 0.012 |
| Low density lipoprotein(mmol/L)        | 2.17 ± 0.79 | 2.20 ± 0.82 | 2.13 ± 0.73 | 0.534 |

Continuous data are presented as means ± standard deviations (SD) or medians (interquartile ranges, IQR) based on the data distribution. Categorical variables are presented as percentages (%). *abc: there is no statistically significant difference between FBG quintiles with the same small letter. BMI, body mass index; FBG, fasting blood glucose.
The constituent ratio of severe and critical cases in each FBG quintile (4.74–5.21, 5.21–5.78, 5.78–7.05, and ≥ 7.05 mmol/L) was 20.7%, 1.7%, 13.8%, 27.1%, and 67.2%, respectively. White bar = cumulatively mild and moderate cases. Black bar = cumulatively severe and critical cases. ns: no significant difference.

### 3.3. Indicators for the risk of severe and critical condition in COVID-19 patients

The factors associated with the risk of severe or critical condition in COVID-19 are presented in Supplementary Table 1. Among those factors, age categories were set at <30, 30–39, 40–49, 50–59, 60–69, 70–79, ≥ 80 years old. BMI, body temperature, CRP, LDH, AST, GTT, TG, and HDL were fitted in quartile categories. The category boundaries of each variable were described in the footnote of Supplementary Table 1. The univariate logistic regression analysis demonstrated a significantly higher odds ratio (OR) of severe or critical condition in COVID-19 patients with older age (OR 1.718, 95%CI 1.393–2.118, P < 0.0001) and elevated BMI (OR 1.570, 95%CI 1.199–2.056, P = 0.001), body temperature (OR 1.996, 95%CI 1.299–3.069, P = 0.002), FBG (OR 1.909, 95%CI 1.579–2.309, P < 0.0001), CRP (OR 1.512, 95%CI 1.019–2.243, P = 0.040), LDH (OR 2.250, 95%CI 1.671–3.030, P < 0.0001), AST (OR 1.662, 95%CI 1.291–2.140, P < 0.0001), and GTT (OR 1.640, 95%CI 1.102–2.441, P = 0.015) levels. Conversely, HDL (OR 0.643, 95%CI 0.497–0.833, P = 0.001) was found to be negatively associated with the risks of patients progressing into severe or critical condition.

Spearman’s bivariate simple correlation analysis demonstrated that FBG levels were positively associated with age (r = 0.425, P < 0.0001), BMI (r = 0.160, P = 0.007), LDH (r = 0.373, P < 0.0001), AST (r = 0.324, P < 0.0001) and GTT (r = 0.233, P = 0.001) levels. Furthermore, FBG levels were significantly negatively associated with HDL levels (r = -0.214, P = 0.001). However, the relationship between FBG levels and body temperature (r = 0.040, P = 0.595), and CRP (r = 0.108, P = 0.149) levels were weak. In addition, we decided to choose the largest contributing variable of liver function test, AST, to enter into each model in the multivariate logistic regression analysis. Together, age, gender, BMI, FBG, HDL, LDH, and AST were used as independent variables in the multivariate step-wise binary logistic regression analysis.

### 3.4. Dose-response relationship of FBG and risk of severe and critical condition in COVID-19

In multivariate logistic regression Model 1, which included FBG quintiles, we observed a significant, J-shaped association between FBG levels across all FBG quintiles and the risk of patients progressing into severe or critical condition. The second quintile was used as the reference, OR (95%CI) of the risk of COVID-19 progressing into severe or critical condition was 15.39 (1.93, 122.72), 1.00 (Reference), 9.63 (1.16, 79.70), 21.95 (2.80, 171.93), 121.11 (15.57, 941.82) in each FBG quintile, respectively (P-trend < 0.001, Table 2). This association was also significant in Model 2 with age, gender, and BMI as additional co-variables (the second quintile was used as the reference, AOR (95%CI) = 19.96 (2.41, 165.36), 1.00 (Reference), 4.89 (0.54, 44.24), 17.49 (2.18, 140.04), 68.11 (8.54, 543.05) per FBG quintile respectively; P-trend < 0.001). Model 3 were fully adjusted for age, gender, BMI, FBG quintile, HDL, LDH, and AST. In Model 3, the second quintile was used as the reference, AOR (95%CI) was 25.33 (2.77, 231.64), 1.00 (Reference), 3.13 (0.33, 29.67), 10.59 (1.23, 91.24), 38.93 (4.36, 347.48) per FBG quintile respectively (P-trend < 0.001). We performed dose–response curves demonstrating visualized evidence of a J-shaped association between FBG levels and risk of severe and critical state in COVID-19 (Fig. 3). In addition, Model 3 shown that age (OR
Table 2 – Multivariable-Adjusted Association of FBG Level and Risk of Severe and Critical Condition for COVID-19 Patients (N = 293).

| FBG quintile (mmol/L) | Median, mmol/L | Model 1 AOR (95% CI) | P | Model 2 AOR (95% CI) | P | Model 3 AOR (95% CI) | P |
|-----------------------|----------------|-----------------------|---|-----------------------|---|-----------------------|---|
| <4.74                 | 4.50           | 15.39 (1.93, 122.72)  | 0.010 | 19.96 (2.41, 165.36)  | 0.006 | 25.33 (2.77, 231.64)  | 0.004 |
| 4.74–5.21             | 5.02           | 1.00 (Ref)            | ND | 1.00 (Ref)            | ND | 1.00 (Ref)            | ND |
| 5.21–5.78             | 5.50           | 9.63 (1.16, 79.70)    | 0.036 | 4.89 (0.54, 44.24)    | 0.158 | 3.13 (0.33, 29.67)    | 0.320 |
| 5.78–7.05             | 6.21           | 21.95 (2.80, 171.93)  | 0.003 | 17.49 (2.18, 140.04)  | 0.007 | 10.59 (1.23, 91.24)   | 0.032 |
| ≥7.05                 | 9.05           | 121.11 (15.57, 941.82)| <0.0001 | 68.11 (8.54, 543.05)  | <0.0001 | 38.93 (4.36, 347.48)  | 0.001 |

FBG data were plotted in quintiles. Model 1 included FBG quintile. Model 2 included FBG quintile, age, gender, and BMI. Model 3 was additionally adjusted for HDL, LDH, and AST levels. FBG, fasting blood glucose; BMI, body mass index; HDL, high-density lipoprotein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; AOR, adjusted odds ratio; ND, not determined; CI, confidence interval; Ref, reference.
To our knowledge, our study provides the first evidence that COVID-19 severity [16]. However, studies into the effects of pre-existing diabetes [7]. Similarly, other research recommends that urine glucose levels be used to differentiate this category. This finding aligns with another recent study aspartate aminotransferase (AST), and high-density lipoprotein (HDL) levels. Additionally adjusted for lactate dehydrogenase (LDH), mass index (BMI). Model 3 (black dotted curve) included FBG quintile, age, gender, and body mass index (BMI). Model 2 (black dashed curve) included FBG quintile, age, gender, and body mass index (BMI). Model 1 (solid black curve) included FBG quintile. Model 2 (black dashed curve) included FBG quintile, age, gender, and body mass index (BMI). Model 3 (black dotted curve) was additionally adjusted for lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and high-density lipoprotein (HDL) levels.

4. Discussion

To our knowledge, our study provides the first evidence that associations between FBG and risk of severe or critical condition were J-shaped for adult, symptomatic COVID-19 patients without diabetes, with a nadir at 4.74–5.78 mmol/L, and varying magnitudes of association. For FBG levels <4.74 mmol/L, FBG was inversely associated with risk of severe and critical condition up to 4.74–5.78 mmol/L with positive association above this point. It is worth noting that there was a substantially higher risk of patients developing severe or critical condition for those with FBG less than 4.74 mmol/L but above the ADA’s hypoglycemia category (the minimum value of FBG in this study was 3.47 mmol/L) [10,11]. This suggests that relatively decreased glucose levels in patients should be a cause for concern. In addition, our AORs for FBG levels ≥7.05 mmol/L suggested highest risk of severe or critical case in this category. This finding aligns with another recent study that claimed that FBG ≥7 mmol/L was an independent risk factor for 28-day mortality in COVID-19 patients without pre-existing diabetes [7]. Similarly, other research recommends that urine glucose levels be used to the differentiate COVID-19 severity [16]. However, studies into the effects of glucose levels on COVID-19 severity generally found linearity [7,16]. It is possible that the relatively small size among COVID-19 populations who with decreased glucose obscures the risk of hypoglycemia for COVID-19 patients.

Many studies have demonstrated that hyperglycemia or diabetes is independent risk factor for the progression and mortality in patients with many infectious diseases such as SARS and COVID-19 [2–7,17]. Immune system dysregulation, rather than actual elevated glucose levels, may be the contributing factor of susceptibility to pathogen infection and severe conditions in diabetes patients [18]. Hyperglycemia, especially in patients without diabetes, may have exacerbated COVID-19 symptoms through separate mechanisms. Early studies have shown that increased levels of serum proinflammatory cytokines are associated with Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) infection [19 20]. More recent studies have shown that patients with COVID-19 also had high amounts of IFN-γ, IL1β, IL6, MCP1, and IP10 [9,21]. In addition, patients requiring ICU admission had higher concentrations of proinflammatory cytokines than did those who did not require going to the ICU, suggesting that the sustained inflammatory response followed by cytokine storm may be associated with COVID-19 severity [21]. Hyperglycemia has been demonstrated to increase inflammatory cytokine levels, oxidative stress and potentially alters the balance between inflammatory and anti-inflammatory cytokines [22]. In addition, innate immune responses to infection have been demonstrated to be altered by acute hyperglycemia, which may in part explain the poor outcomes in COVID-19 patients who develop hyperglycemia [23,24]. Furthermore, elevated glucose concentrations in airway epithelial secretion may damage the defensive capacity of airway epithelia [25].

Unfortunately, we had no data about pancreas islet function in this study, otherwise we could have further explored the mechanisms underlying hyperglycemia. Previous studies reported that acute viral respiratory infection has been related to transiently decreased insulin sensitivity [26]. Moreover, angiotensin-converting enzyme-2 (ACE-2) receptors are expressed in pancreatic islets. It has been reported that individuals infection with SARS-CoV-1 developed hyperglycemia [27]. Further studies with large patient cohorts will be required to properly evaluate pancreas islet function in patients with COVID-19.

Hyperglycemia can cause acute harm to patients and in severe cases can lead to loss of consciousness, seizure, coma, or death [10,12]. It has been demonstrated that the replication of SARS-CoV-2 viruses consumes substantial amount of ATP in the body [28] so is logical to imagine that patients with decreased blood glucose may have fewer energetic resources to provide for the energy needed at cellular level work to fight acute levels of viral infection. In addition, glucose can be oxidized through a pentose phosphate pathway, yielding nicotinamide adenine dinucleotide phosphate (NADPH), thus maintaining the reducing state of glutathione (GSH). Reduced glutathione works for the anti-oxidant defense system and works with the immune system to fight invasive pathogenic microorganisms [28,29]. On the cellular level, blood glucose is largely required for activated immune cells to mount a robust response [29]. These processes together indicate that
comparatively low blood glucose levels result in enhanced oxidative stress and impaired immune responses. Collectively, until it is proven not to be causal, it is prudent to avoid hypoglycemia regardless of the cause of the condition in COVID-19 patients. Collectively, it is prudent to avoid hypoglycemia regardless of its cause in COVID-19 patients.

Various studies agreed with our finding patients increased levels of CRP, and LDH were associated with the severity of COVID-19 patients, particular in middle-aged men [8,9,14,21,30]. In addition, we found that BMI had an inverse effect on severe and critical condition in COVID-19 patients. Indeed, obesity has been demonstrated as a risk factor for increasing severity of SARS-CoV-2-related illness [31]. Here, we demonstrated for the first time that HDL can be used as a protective factor for preventing COVID-19 exacerbation. Consistent with this finding, there are studies supporting the anti-inflammatory effects of HDL [32].

We acknowledge that our sample size limited the glycemic target research for COVID-19 patients with diabetes. More solid estimates of optimal glycemic target of COVID-19 will be determined through analyses of larger sample size cohorts and related quality data. Indeed, Li et al. provided clinical evidence for glycemic target within 3.9–10.0 mmol/L for COVID-19 patients with diabetes [33]. However, our study did show a relevant effect of appropriate glycemic target on the risk of confirmed severity and criticality of COVID-19 in non-diabetes patients supporting the need to continue this area of study to provide more robust guidance for managing the COVID-19 pandemic. Ideally, continuous glucose monitoring (CGM) should be used to identify characteristics of glycaemia that are associated with severity of COVID-19. However, we had insufficient data about CGM in this study due to the different management plan in multiple hospitals. In addition, the research design could have resulted in selection bias as all subjects were Han Chinese and enrolled from one city, which weakens the generalizability of the results to other races. Furthermore, being a cross-sectional study, cause–causality relationships and mechanisms underlying the association between FBG and risk of COVID-19 exacerbation is difficult to elucidate.

In conclusion, the associations between FBG and risk of severe and critical condition were J-shaped for non-diabetes adult patients with COVID-19, with nadir at 4.74–5.78 mmol/L.

Funding information
This work was supported by the National Key R&D Program of China (No. 2018YFC1314101; 2016YFC1305600), the National Natural Science Foundation of China (No. 81970677), and the Key Scientific and Technological Innovation Projects of Wenzhou (ZYY202004). The funders had no role in the design and conduct of the study, the completion of the analysis, the interpretation of the data, or the content and preparation of the manuscript.

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.

Acknowledgements
The authors would like to acknowledge Li Ming Wen (School of Public Health, University of Sydney, Australia) for his kind support for editing and proofreading this manuscript.

Appendix A. Supplementary material
Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108381.

REFERENCES

[1] Weiss P et al. Murdoch DR Clinical course and mortality risk of severe COVID-19. Lancet 2020;395:1014–5. https://doi.org/10.1016/S0140-6736(20)30633-4.
[2] Singh AK et al. Khunti K Assessment of risk, severity, mortality, glycemic control and anti-diabetic agents in patients with diabetes and COVID-19: a narrative review. Diabetes Res Clin Pract 2020;165. https://doi.org/10.1016/j.drcps.2020.101678.
[3] Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020. https://doi.org/10.1002/dmrr.3319 e3319.
[4] Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31(1068–1077). https://doi.org/10.1016/j.cmet.2020.04.021 e1063.
[5] Singh AK, Gupta R, Ghosh A, et al. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr 2020;14:303–10. https://doi.org/10.1016/j.dsx.2020.04.004.
[6] Sardu C, D’Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycaemia affected by COVID-19: can we do more on glycemic control? Diabetes Care 2020;43:1408–15. https://doi.org/10.2337/dc20-0723.
[7] Wang S, Ma P, Zhang S, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. Diabetologia 2020. https://doi.org/10.1007/s00125-020-05209-1.
[8] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected
pneumonia in Wuhan, China. JAMA 2020. https://doi.org/10.1001/jama.2020.1585.

[9] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13. https://doi.org/10.1016/S0140-6736(20)30211-7.

[10] American Diabetes A. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018; 41: S55–64. Doi: 10.2337/dc18-5006.

[11] International Hypoglycaemia Study G. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017; 40: 155–157. Doi: 10.2337/dc16-2215.

[12] Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–8. https://doi.org/10.1056/NEJMoa1003795.

[13] Forbes A, Murrells T, Mulnier H, et al. Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. Lancet Diabetes Endocrinol 2018;6:476–86. https://doi.org/10.1016/S2213-8587(18)30049-2.

[14] Han Y, Liu Y, Zhou L, et al. Epidemiological assessment of imported coronavirus disease 2019 (COVID-19) cases in the most affected city outside of Hubei Province, Wenzhou, China. JAMA Netw Open 2020;3. https://doi.org/10.1001/jamanetworkopen.2020.6785.

[15] Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;20:689–96. https://doi.org/10.1016/S1473-3099(20)30198-5.

[16] Liu R, Ma Q, Han H, et al. The value of urine biochemical parameters in the prediction of the severity of coronavirus disease 2019. Clin Chem Lab Med 2020. https://doi.org/10.1126/science.aar3932.

[17] Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623–8. https://doi.org/10.1111/j.1464-5491.2006.01861.x.

[18] Hodgson K, Morris J, Bridson T, et al. Immunological mechanisms contributing to the double burden of diabetes and intracutaneous bacterial infections. Immunology 2015;144:171–85. https://doi.org/10.1111/imn.12394.

[19] Falzarano D, de Wit E, Rasmussen AL, et al. Treatment with interferon-alpha2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013;19:1313–7. https://doi.org/10.1038/nm.3362.

[20] Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004;136:95–103. https://doi.org/10.1111/j.1365-2249.2004.02415.x.

[21] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[22] Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067–72. https://doi.org/10.1161/01.cir.0000034509.14906.ae.

[23] Dasu MR, Devaraj S, Zhao L, et al. High glucose induces toll-like receptor expression in human monocytes: mechanism of activation. Diabetes 2008;57:3090–8. https://doi.org/10.2337/db08-0564.

[24] Jafar N, Edriss H, et al. The effect of short-term hyperglycemia on the innate immune system. Am J Med Sci 2016;351:201–11. https://doi.org/10.1016/j.amjms.2015.11.011.

[25] Philips BJ, Meguer JX, Redman J, et al. Factors determining the appearance of glucose in upper and lower respiratory tract secretions. Intensive Care Med 2003;29:2204–10. https://doi.org/10.1007/s00134-003-1961-2.

[26] Sestan M, Marinovic S, Kavazovic I, et al. Virus-induced interferon-gamma causes insulin resistance in skeletal muscle and derails glycemic control in obesity. Immunity 2018;49(164–177). https://doi.org/10.1016/j.immuni.2018.05.005.

[27] Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–9. https://doi.org/10.1007/s00592-009-0109-4.

[28] Li Z, Liu G, Wang L, et al. From the insight of glucose metabolism disorder: oxygen therapy and blood glucose monitoring are crucial for quarantined COVID-19 patients. Ecotoxicol Environ Saf 2020;197. https://doi.org/10.1016/j.ecoenv.2020.110614.

[29] Wang A, Luan HH, et al. An evolutionary perspective on immunometabolism. Science 2019;363. https://doi.org/10.1126/science.aar3932.

[30] Yang J-K, Jin J-M, Liu S, et al. Blood glucose is a representative of the clustered indicators of multi-organ injury for predicting mortality of COVID-19 in Wuhan, China. medRXiv 2020. https://doi.org/10.1101/2020.04.08.20058040.

[31] Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa415.

[32] De Nardo D, Labzin LI, Kono H, et al. High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat Immunol 2014;15:152–60. https://doi.org/10.1038/ni.2784.

[33] Lihua Zhu Z-GS, Cheng Xu, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31:1–10.