Fasting blood glucose level is a predictor of mortality in patients with COVID-19 independent of diabetes history

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ABSTRACT

Aim: No study elucidated the role of fasting blood glucose (FBG) level in the prognosis of coronavirus disease 2019 (COVID-19).

Methods: This cohort study was conducted in a single center at Renmin Hospital of Wuhan University, Wuhan, China. Clinical laboratory, and treatment data of inpatients with laboratory-confirmed COVID-19 were collected and analyzed. Outcomes of patients with and without pre-existing diabetes were compared. The associations of diabetes history and/or FBG levels with mortality were analyzed. Multivariate cox regression analysis on the risk factors associated with mortality in patients with COVID-19 was performed.

Results: A total of 941 hospitalized patients with COVID-19 were enrolled in the study. There was a positive relationship between pre-existing diabetes and the mortality of patients who developed COVID-19 (21 of 123 [17.1%] vs 76 of 818 [9.3%]; P = 0.012). FBG ≥7.0 mmol/L was an independent risk factor for the mortality of COVID-19 regardless of the presence or not of a history of diabetes (hazard ratio, 2.20 [95% CI, 1.21–4.03]; P = 0.010).

Conclusions: We firstly showed FBG ≥7.0 mmol/L predicted worse outcome in hospitalized patients with COVID-19 independent of diabetes history. Our findings indicated screening FBG level is an effective method to evaluate the prognosis of patients with COVID-19.

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1. Introduction

The COVID-19 pandemic, which caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is a novel and serious global health threat and dramatically spreads worldwide [1].

Diabetes has been uniformly reported to be associated with poor prognosis in coronavirus infections. One retrospective analysis suggested that a known history of diabetes and ambient hyperglycemia were independent predictors for death and morbidity in SARS patients [2]. Diabetes was prevalent in approximately 50% of the patients with MERS-CoV in a

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systematic analysis of 637 cases [3]. Recent clinical studies confirmed diabetes as a major comorbidity of COVID-19 [4–7]. Guo et al. [8] and Dong et al. [9] had investigated the correlation between diabetes history and prognosis of COVID-19, which analyzed 174 and 193 patients with COVID-19 respectively. However, no study focused on the direct correlation between fasting blood glucose (FBG) levels and the prognosis of COVID-19. Furthermore, whether diabetes history or blood glucose level is more important for mortality of patients with COVID-19 remains unclear. In the present research, we investigated the clinical characteristics of patients with coexistence of COVID-19 infection and diabetes, and examined the associations of diabetes history and/or FBG levels with the mortality of COVID-19 in a selected cohort of patients in Wuhan, China.

2. Materials and methods

2.1. Study design and participants

This is a retrospective, single center study at Renmin Hospital of Wuhan University in Wuhan, China. The hospital had assigned responsibility for the treatment of patients with severe COVID-19 by the Wuhan government. All enrolled patients were definitively diagnosed based on the criteria for COVID-19 (trial version 6) established by the Chinese National Health Commission. Exclusion criterions included: (1) Mild cases, which defined as mild clinical manifestation and no obvious chest CT findings for COVID-19; (2) Duplicated cases; (3) No available core medical information. Patients were consecutive admitted to hospital from January 20 to February 20, 2020. All included cases were shared with WHO. The final date of follow-up was March 3, 2020. This study was approved by the National Health Commission of China and the institutional review board at Renmin Hospital of Wuhan University. Written informed consent was waived by the ethics commission of the designated hospital for patients with emerging infectious diseases.

2.2. Data collection

We obtained clinical, laboratory, radiological, treatment, and outcome data from patients' electronic medical records for hospitalized patients. All data were reviewed by two investigators (F.Y. and B.Y.). Patients' diabetes history information was collected, and FBG levels were measured on admission. The normal reference range of FBG in Renmin hospital of Wuhan University is 3.9–6.1 mmol/L. As FBG $\geq$ 7.0 mmol/l is one of diagnostic criterions of diabetes, we took 7.0 mmol/l as a cut-point for the FBG levels. Clinical data included symptoms and comorbidities. Laboratory assessments included complete blood count, c-reactive protein (CRP), procalcitonin (PCT), electrolytes, liver and renal function values. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [10]. Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition [11].

To confirm COVID-19, the Viral Nucleic Acid Kit (Health, Ningbo, China) was used to extract nucleic acids from throat swab, nose swab, anal swab, or phlegm samples according to the kit instructions. A 2019-nCoV detection kit (Bioperfectus, Taizhou, China) was used to detect the ORF1ab gene (nCovOR-F1ab) and the N gene (nCoV-NP) according to the manufacturer's instructions using real-time RT-PCR [12]. An infection was considered as laboratory-confirmed if the nCovORF1ab and nCoV-NP both showed positive results.

2.3. Statistical analysis

Descriptive statistics were obtained for all study variables. All categorical variables were compared for the study outcome by using the Fisher's exact test, and continuous variables were compared using the Student t test or the Mann-Whitney U test, if appropriate. Continuous data are expressed as mean ± standard deviation (SD) or median (interquartile ranger, IQR). Categorical data were expressed as the counts and proportion. Survival curves were plotted using the Kaplan-Meier method. Univariate and multivariate cox regression models were used to determine the independent risk factors for death during hospitalization, with a time from admission to the end of follow-up. The cases missing biomarker data were excluded listwise with statistics software. Data were analyzed using SPSS 25.0 (IBM, Chicago, IL). Statistical charts were generated using Excel 2016, Graphpad Prism (Version 5.0, GraphPad Software) or Minitab (Version 18, Minitab statistical Software). For all the statistical analyses, p < 0.05 was considered significant.

3. Results

3.1. Patients Characteristics

Supplementary Fig. 1 depicts a flowchart for patient recruitment. Briefly, a total of 2157 patients with confirmed COVID-19 were screened initially, from January 20, 2020, to February 20, 2020, 1074 mild cases, 142 duplicated cases and cases without available medical information were excluded. 941 cases (death, 97; survival, 844) with COVID-19 were included in final analysis. Of these patients, 123 patients (13.1%) had a history of diabetes and 818 patients (86.9%) did not have pre-existing diabetes; 242 patients (25.7%) had FBG equal or greater than 7 mmol/L and 699 patients (74.3%) had FBG lower than 7 mmol/L. The median age was 57 years (range, 18–98 years), and 487 (51.8%) were female. Among these patients, the most common symptom at onset of illness was fever (687 patients [73.0%]). Less common symptoms were cough (315 patients [33.5%]), shortness of breath (232 patients [24.7%]), and fatigue (133 patients [14.1%]). Sputum production 40 patients (4.3%), chest pain (34 patients [3.6%]), diarrhea (27 patients [2.9%]), and headache (20 patients [2.1%]) were rare. Comorbidities were present in 586 patients. Other than diabetes, hypertension was the most common comorbidity (272 patients [28.9%]), followed by coronary heart disease (74 patients [7.9%]) and cerebrovascular disease (64 patients [6.8%]). The proportion of chronic renal failure, chronic obstructive pulmonary disease (COPD), cancer, chronic heart failure, hepatitis B infection pregnancy and pregnancy was 4.7% (44 patients), 3.7% (35 patients), 3.0%
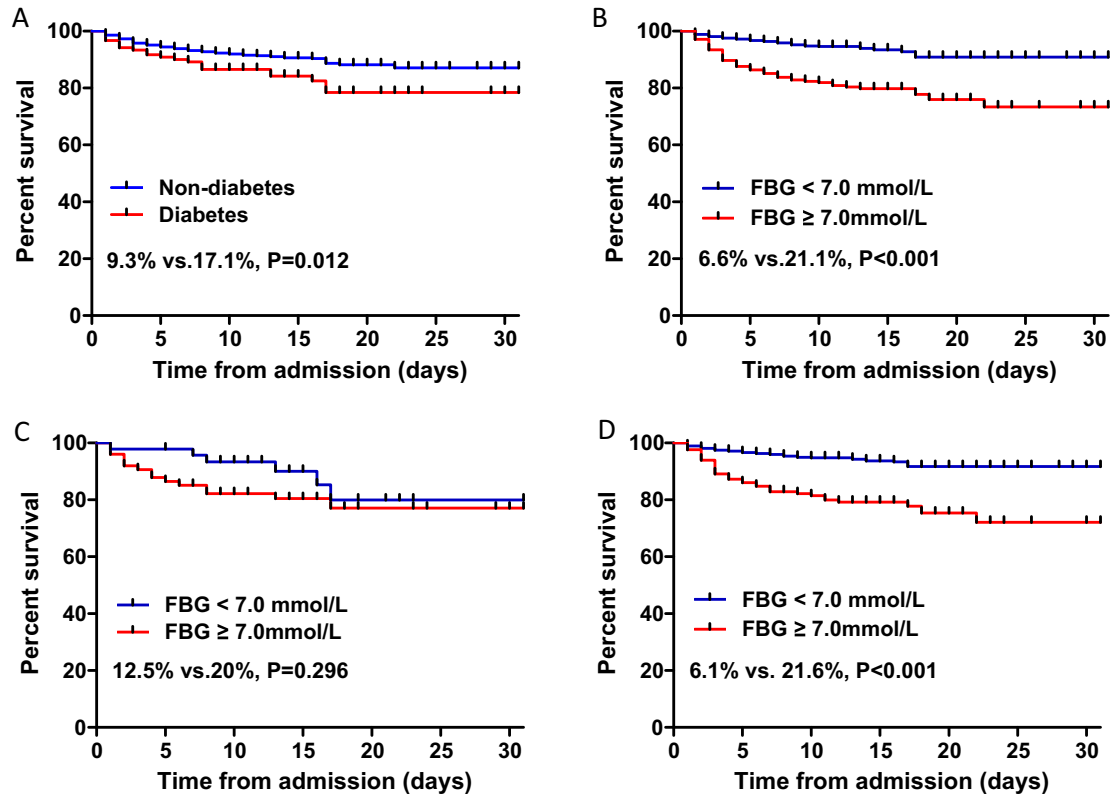
Fig. 1 – Kaplan-Meier survival curves of survival probability in hospitalized patients with COVID-19. A. Mortality was higher in patients with diabetes. B. Mortality was significantly higher in patients with FBG ≥ 7.0 mmol/l. C. Among diabetes subjects, mortality was higher in patients with FBG ≥ 7.0 mmol/L, there was no statistical difference after log-rank test. D. Among non-diabetes subjects, the mortality was significantly higher in patients with FBG ≥ 7.0 mmol/L. FBG, fasting blood glucose.

(28 patients), 2.9% (27 patients), 2.6% (24 patients), and 1.9% (18 patients), respectively (Table 1).

Compared with patients without pre-existing diabetes, patients with diabetes were in older ages (median [range], 69[27–99] years vs 56 [18–95] years; P < 0.001), and more likely to have shortness of breath (40 [32.5%] vs 192 [23.5%]). Moreover, patients with diabetes had more underlying comorbidities, including hypertension (66 [53.7%] vs 206 [25.2%]), coronary heart disease (19 [15.4%] vs 55 [6.7%]), chronic renal failure (16 [13.0%] vs 28 [3.4%]) and chronic heart failure (11 [8.9%] vs 16 [2.0%]) (Table 1).

Compared with patients with FBG < 7.0 mmol/L, patients with FBG ≥ 7.0 mmol/l were older (median [range], 64 [31–98] years vs 56 [18–95] years; P < 0.001), and more likely to have shortness of breath (87 [36.0%] vs 145 [20.7%]) and feel fatigue (46 [19.0%] vs 87 [12.4%]). Patients with hyperglycemia showed more comorbidities, including hypertension (108 [44.6%] vs 164 [23.5%], coronary heart disease (29 [12.0%] vs 45 [6.4%]), chronic renal failure (22 [9.1%] vs 22 [3.1%]) and chronic heart failure (17 [7.0%] vs 10 [1.4%]). Additionally, the FBG levels of all pregnancy patients were lower than 7 mmol/L. (Table 1).

3.2. Laboratory findings

On admission, in the overall study population of 941 patients, median (IQR) levels of FBG (6.5 [5.2–8.3] mmol/L) and CRP (44.3 [15.4–81.4] mg/L) were elevated whereas the proportion of lymphocytes was declined (15.7 [8.6–23.6]%). The median values of other laboratory indicators were within the normal range, such as counts of leucocytes, platelets, erythrocytes and the levels of hemoglobin, alanine aminotransferase, aspartate aminotransferase, creatinine and electrolyte. The proportion of patients with bilateral pneumonia was 57.5% (541 patients) according to chest radiography and computed tomography findings. Also, 224 patients (23.8%) had multiple mottling and ground-glass opacity (Table 1).

Compared with patients who did not have history of diabetes, patients with diabetes showed higher median (IQR) levels of FBG (9.5[7.3–14.8] mmol/L vs 6.1[5.1–7.6] mmol/L), CRP (57.7 [22.6–86.9] mg/L vs 42 [14.4–80.8] mg/L), PCT (0.1 [0.05–0.32] ng/mL vs 0.06 [0.04–0.14] ng/mL), potassium (4.1 [3.5–5.7] mmol/L vs 3.9[3.4–4.2] mmol/L), but a lower proportion of lymphocytes (12.2[7.9–20.7]% vs 16[8.7–23.9]%). With regards to radiologic findings, bilateral pneumonia in patients

Table 1 – Baseline Characteristics, Laboratory and Radiographic findings of 941 Patients with COVID-19.

Characteristics	All (n = 941)	Diabetes (n = 123)	Non-diabetes (n = 818)	P value	FBG ≥ 7.0 mmol/l (n = 242)	FBG < 7.00 mmol/l (n = 699)	P value
Age (yrs), Median (range)	57(18–98)	69(27–99)	56(18–95)	<0.001	64 (31–98)	56 (18–95)	<0.001
Female, n (%)	487(51.8)	62(50.4)	425(52.0)	0.772	119 (49.2)	368 (52.6)	0.351
Signs and symptoms at admission, n (%)							
Fever	687(73.0)	87(70.7)	600(73.3)	0.586	183 (75.6)	504(72.1)	0.288
Cough	315(33.5)	43(35.0)	272(33.3)	0.759	90 (37.2)	225 (32.2)	0.155
Shortness of breath	232(24.7)	40(32.5)	192(23.5)	0.033	87 (36.0)	145 (20.7)	<0.001
Fatigue	133(14.1)	18(14.6)	115(14.1)	0.89	46 (19.0)	87 (12.4)	0.012
Sputum production	40(4.3)	6(4.9)	34(4.2)	0.636	12 (5.0)	28 (4.0)	0.527
Chest pain	34(3.6)	1(0.8)	33(4.0)	0.113	4 (1.7)	30 (4.3)	0.058
Diarrhea	27(2.9)	3(2.4)	24(2.9)	1.000	4 (1.7)	23 (3.3)	0.188
Headache	20(2.1)	2(1.6)	18(2.2)	1.000	4 (1.7)	16 (2.3)	0.554
Chronic medical illness, n (%)							
Hypertension	272(28.9)	66(53.7)	206(25.2)	<0.001	108 (44.6)	164 (23.5)	<0.001
Coronary heart disease	74(7.9)	19(15.4)	55(6.7)	0.002	29 (12.0)	45 (6.4)	0.006
Cerebrovascular disease	64(6.8)	10(8.1)	54(6.6)	0.563	18 (7.4)	46 (6.6)	0.648
Chronic renal failure	44(4.7)	16(13.0)	28(3.4)	<0.001	22 (9.1)	22 (3.1)	<0.001
COPD	35(3.7)	6(4.9)	29(3.5)	0.444	12 (5.0)	23 (3.3)	0.237
Cancer	28(3.0)	5(4.1)	23(2.8)	0.398	9 (3.6)	19 (2.7)	0.492
Chronic heart failure	27(2.9)	11(8.9)	16(2.0)	<0.001	17 (7.0)	10 (1.4)	<0.001
Hepatitis B infection	24(2.6)	4(3.3)	20(2.4)	0.542	10 (4.1)	14 (2.0)	0.070
Pregnancy	18(1.9)	1(0.8)	17(2.1)	0.495	0 (0)	18 (2.6)	0.012
Laboratory findings at admission, median (IQR)							
Leucocytes ($\times 10^9$/L)	6(4.3–8.8)	6.2(4.6–9.2)	5.9(4.2–8.8)	0.254	7.1 (5.0–11.0)	5.4 (4.0–8.1)	<0.001
Lymphocytes (%)	15.7(8.6–23.6)	12.2(7.9–20.7)	16(8.7–23.9)	0.033	10.3 (5.9–15.9)	18.5 (11.1–25.5)	<0.001
Platelets ($\times 10^9$/L)	207(149–280)	189(126–262)	211(152–281)	0.095	194 (133–261)	211.5 (155–285)	0.034
Erythrocytes ($\times 10^{12}$/L)	3.9(3.5–4.3)	3.8(3.4–4.2)	3.9(3.5–4.3)	0.432	3.9 (3.5–4.3)	3.9 (3.5–4.3)	0.863
Haemoglobin (g/L)	121(109–132)	120(109–130)	121(110–132)	0.941	122 (111–133)	120 (108–131)	0.145
C-reactive protein (mg/L)	44.3(15.4–81.4)	57.7(22.6–86.9)	42(14.4–80.8)	0.039	68.2 (27.4–114.2)	36.6 (12.4–66.9)	<0.001
Procalcitonin (ng/mL)	0.07(0.04–0.16)	0.1(0.05–0.32)	0.06(0.04–0.14)	0.001	0.13 (0.05–0.46)	0.06 (0.03–0.09)	<0.001
ALT (U/L)	33(20–61)	34(21–56)	33(20–62)	0.747	35 (21–68)	32 (19–69)	0.142
AST (U/L)	33(22–51)	31(23–48)	33(22–51)	0.596	38 (24–60)	31 (21–47)	0.001
Creatinine (μmol/L)	59(49–74)	61(51–89)	59(48–73)	0.214	61 (51–87)	57 (48–71)	0.014
FBG (mmol/L)	6.5(5.2–8.3)	9.5(7.3–14.8)	6.1(5.1–7.6)	<0.001	9.0 (7.8–11.9)	5.4 (4.9–6.1)	<0.001
Potassium (mmol/L)	3.9(3.5–4.3)	4.1(3.5–4.7)	3.9(3.4–4.2)	0.036	3.9 (3.4–4.6)	3.9 (3.5–4.2)	0.800
Sodium (mmol/L)	140(137–143)	139(136–143)	140(137–144)	0.064	139 (135–143)	140 (137–144)	0.005
Chest X-ray and CT findings, n (%)							
Unilateral pneumonia	400(42.5)	37(30.1)	363(44.4)	0.003	64 (26.4)	336 (48.1)	<0.001
Bilateral pneumonia	541(57.5)	86(69.9)	455(55.6)		178 (73.6)	363 (51.9)	
Multiple mottling and ground-glass opacity	224(23.8)	37(30.1)	187(22.9)	0.088	61 (25.2)	163 (23.3)	0.552

yrs, years; IQR, interquartile range; COPD, Chronic obstructive pulmonary disease; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FBG, fasting blood glucose; CT, computed tomography.

Characteristics	All (n = 941)	Diabetes (n = 123)	Non-diabetes (n = 818)	P value	FBG ≥ 7.0 mmol/l (n = 242)	FBG < 7.00 mmol/l (n = 699)	P value
Time from symptom onset to admission (days), Median (IQR)	10(7–14)	10(7–15)	10(7–14)	0.216	10 (7–14)	10 (7–13)	0.050
Treatment, n (%)							
Oxygen inhalation	800(85.0)	83(67.5)	717(87.7)	<0.001	168 (69.4)	632 (90.4)	<0.001
Non-invasive ventilation	79(8.4)	27(22.0)	52(6.4)	<0.001	34 (14.0)	45 (6.4)	<0.001
Invasive mechanical ventilation	40(4.3)	11(8.9)	29(3.5)	0.013	25 (10.3)	15 (2.1)	<0.001
Continuous renal replacement therapy	2(0.2)	1(0.8)	1(0.1)	0.244	2 (0.8)	0 (0)	0.016
Antiviral treatment	813(86.4)	105(85.4)	708(86.6)	0.675	211 (87.2)	602 (86.1)	0.676
Glucocorticoids	363(38.6)	50(40.7)	313(38.3)	0.62	102 (42.1)	261 (37.3)	0.185
Intravenous immunoglobulin therapy	151(16.0)	20(16.3)	131(16.0)	0.896	49 (20.2)	102 (14.6)	0.039
Antibiotic treatment	455(48.4)	58(47.2)	397(48.5)	0.847	126 (52.1)	329 (47.1)	0.180
Complications, n (%)							
ARDS	185(19.7)	47(38.2)	138(16.9)	<0.001	71 (29.3)	114 (16.3)	<0.001
Acute respiratory failure	79(8.4)	13(10.6)	66(8.1)	0.382	43 (17.8)	36 (5.2)	<0.001
Acute kidney injury	40(4.3)	10(8.1)	30(3.7)	0.03	18 (7.4)	22 (3.1)	0.004
Acute heart failure	29(3.1)	8(6.5)	21(2.6)	0.043	20 (8.3)	9 (1.3)	<0.001
Electrolyte disturbance	130(13.8)	18(14.6)	112(13.7)	0.779	50 (20.7)	80 (11.4)	<0.001
Hypoproteinemia	80(8.5)	21(17.1)	59(7.2)	0.001	32 (13.2)	48 (6.9)	0.002

Table 2 – Treatment, Complications and Clinical Outcomes of 941 Patients with COVID-19.

ARDS, acute respiratory distress syndrome;

with diabetes was more prevalent than in patients without diabetes (86 of 123 [69.9%] vs 455 of 818 [55.6%]) (P = 0.003, Table 1).

Compared with patients with FBG < 7.0 mmol/L, patient with FBG ≥ 7.0 mmol/L had higher median (IQR) levels of FBG (9.0 [7.8–11.9] mmol/L vs 5.4 [4.9–6.1] mmol/L), leucocytes (7.1 [5.0–11.0] × 10^9/L vs 5.4 [4.0–8.1] × 10^9/L), CRP (68.2 [27.4–114.2] mg/L vs 36.6 [12.4–66.9] mg/L), PCT (0.13 [0.05–0.46] ng/mL vs 0.06 [0.03–0.09] ng/mL), AST (38 [24–60] U/L vs 31 [21–47] U/L), creatinine (61 [51–87] μmol/L vs 57 [48–71] μmol/L), but a lower proportion of lymphocytes (10.3 [5.9–15.9]% vs 18.5 [11.1–25.5]%), lower levels of platelets (194 [133–261] × 109/L vs 211.5 [155–285] × 109/L), sodium (139 [135–143] mmol/L vs 140 [137–144] mmol/L). With regards to radiologic findings, bilateral pneumonia in patients with FBG ≥ 7.0 mmol/L was more prevalent than in patients with FBG < 7.0 mmol/L (178 of 242 [73.6%] vs 363 of 699 [51.9%]) (P < 0.001, Table 1).

3.3.   Treatment and complications

All patients were treated in isolation. The median duration from symptom onset to admission was 10 (IQR, 7–14) days. A total of 919 patients (97.7%) were treated with oxygen. The percentages of use of oxygen inhalation, noninvasive ventilation, and invasive mechanical ventilation were 85.0% (800 patients), 8.4% (79 patients), and 4.3% (40 patients), respectively. The proportion of antiviral therapy use was the highest (813 [86.4%]), followed by antibiotic therapy (455 [48.4%]), glucocorticoids (363 [38.6%]), and intravenous immunoglobulin therapy (151 [16%]). Only 2 patients (0.2%) among all participants were given continuous kidney therapy. Overall, 185 patients (19.7%) had ARDS, 130 patients had electrolyte disturbance (13.8%), and 79 patients (8.4%) had acute respiratory failure during hospitalization. Other common complications included hypoproteinemia (80 [8.5%]), acute kidney injury (40 [4.3%]), and acute heart failure (29 [3.1%]) (Table 2).

Compared with those without history of diabetes, patients with diabetes required more noninvasive ventilation (27 [22.0%] vs 52 [6.4%]; P < 0.001) and invasive mechanical ventilation (11 [8.9%] vs 29 [3.5%]; P < 0.013) (Table 2). With regards to complications, patients with diabetes were more likely to develop ARDS (47 [38.2%] vs 138 [16.9%]; P < 0.001), acute kidney injury (10 [8.1%] vs 30 [3.7%]; P = 0.03) and acute heart failure (8 [6.5%] vs 21 [2.6%]; P = 0.043) than those without diabetes (Table 2).

Compared with patients with FBG < 7.0 mmol/L, patients with FBG ≥ 7.0 mmol/L required more noninvasive ventilation (34 [14.0%] vs 45 [6.4%]; P < 0.001), invasive mechanical ventilation (25 [10.3%] vs 15 [2.1%]; P < 0.001), continuous renal replacement therapy (2 [0.8%] vs 0 [0%]; P = 0.016), and intravenous immunoglobulin therapy (49 [20.2%] vs 102 [14.6%]; P < 0.001) (Table 2). With regards to complications, patients with hyperglycemia were more likely to develop ARDS (71 [29.3%] vs 114 [16.3%]; P < 0.001), acute respiratory failure (43 [17.8%] vs 36 [5.2%]; P < 0.001), acute kidney injury (18 [7.4%] vs 22 [3.1%]; P = 0.004), acute heart failure (20 [8.3%] vs 9 [1.3%]; P < 0.001), electrolyte disturbance (50 [20.7%] vs 80 [11.4%]; P < 0.001) and hypoproteinemia (32 [13.2%] vs 48 [6.9%]; P = 0.002) than those with FBG < 7.0 mmol/L (Table 2).

3.4.   Diabetes, FBG and mortality

On Kaplan-Meier analysis, the mortality in patients with pre-existing diabetes was higher than that in patients without pre-existing diabetes (21/123 [17.1%] vs 76/818 [9.3%]; P = 0.012) (Fig. 1A). The mortality difference was more pronounced between patients with FBG higher and lower than 7 mmol/L (/51/245[20.1%] vs 46/696[6.6%]; P < 0.001) (Fig. 1B).

Among diabetes subjects, the mortality in patients with FBG ≥ 7.0 mmol/L (15/75 [20%]) was higher than that in patients with FBG < 7.0 mmol/L (6/48 [12.5%]), however, there was no significant difference after log-rank test (P = 0.296) (Fig. 1C). Among non-diabetes subjects, the mortality in patients with FBG ≥ 7.0 mmol/L was remarkably higher than that in patients with FBG < 7.0 mmol/L (36/167 [21.6%] vs 40/651[6.1%]; P < 0.001) (Fig. 1D).

We performed a contour plot to determine the relationship between levels of FBG or age and mortality. Overall, the death rate of older patients was higher, especially for the age was greater than 60 years old (Fig. 2A). For patients with history of diabetes, high mortality was much closely correlated with hyperglycemia (Fig. 2B). For patients without diabetes, higher mortality was also, to certain extent, related with hyperglycemia (Fig. 2C).

After adjusting age, sex, most common comorbidities of COVID-19, inflammatory indicators and FBG levels, the univariate adjusted cox proportional hazard regression model revealed a significantly higher risk of death in COVID-19 patients with senior age, hypertension, diabetes, coronary heart disease, cerebrovascular disease, chronic renal failure, COPD, chronic heart failure, high levels of CRP and PCT, FBG ≥ 7 mmol/L. In multivariable cox regression analysis, age (hazard ratio [HR], 1.04; 95% confidence interval [CI], 1.01–1.06), hypertension (HR, 1.89; 95%CI, 1.04–3.45), coronary heart disease (HR, 0.42; 95%CI, 0.18–0.96), chronic renal failure (HR, 3.17; 95%CI,1.48–6.80), chronic heart failure (HR, 3.44; 95% CI, 1.52–7.83), CRP (HR, 1.01; 95%CI, 1.00–1.01), and FBG ≥ 7.0 mmol/L (HR, 2.20; 95%CI, 1.21–4.03) were independent risk factors of mortality in patients with COVID-19 (Table 3).

4.   Discussion

In this retrospective analysis, we found that there was a positive relationship between pre-existing diabetes and the mortality of patients who developed COVID-19, however, the diabetes history was not an independent risk factor of death rate in patients with COVID-19. More importantly, the present study was the first to show that FBG ≥ 7.0 mmol/L was a predictor of mortality in patients with COVID-19 independent of diabetes history. Besides that, patients with diabetes revealed senior age and much severer inflammatory responses, as well as increased incidences of comorbidities and complications compared with those without diabetes. When grouped by FBG levels, in addition to above difference, patients with FBG ≥ 7.0 mmol/L required more treatment than patients with FBG < 7.0 mmol/L.

It was reported that glucose control is associated with different outcomes in patients with COVID-19 and pre-existing diabetes [13]. A recent study, which included 47 patients,
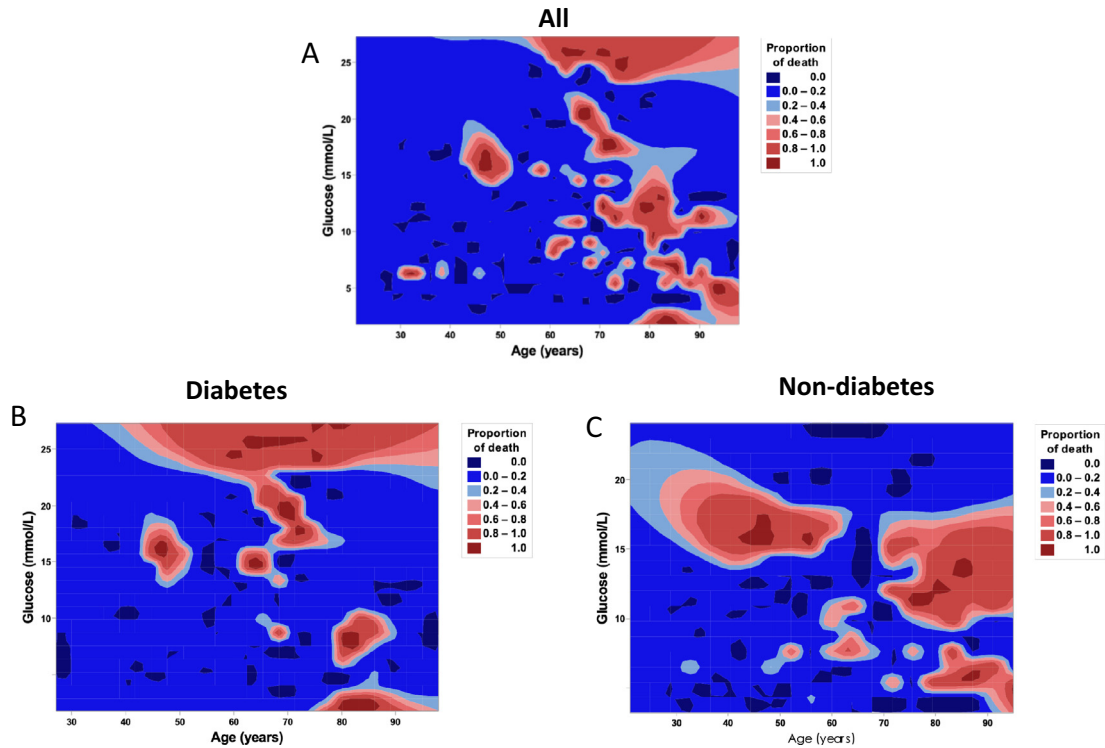
Fig. 2 – Contour plot of survival probability in hospitalized patients with COVID-19. A. Mortality was higher in patients with senior age. B. In diabetes group, mortality was higher in patients with hyperglycemia. C. In non-diabetes group, mortality was higher in patients with hyperglycemia and senior age. FBG, fasting blood glucose.

Table 3 – Univariate and multivariate cox regression analysis on the risk factors associated with mortality in patients with COVID-19.

Characteristics	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Male	0.81	0.55–1.21	0.312	0.90	0.50–1.63	0.729
Age	1.07	1.05–1.08	<0.001	1.04	1.01–1.06	0.004
Hypertension	2.76	1.85–4.12	<0.001	1.89	1.04–3.45	0.037
Diabetes	1.78	1.10–2.89	0.019	0.67	0.32–1.39	0.280
Coronary heart disease	3.05	1.88–4.95	<0.001	0.42	0.18–0.96	0.041
Cerebrovascular disease	0.20	0.11–0.36	<0.001	0.75	0.30–1.87	0.534
Chronic renal failure	4.17	2.36–7.35	<0.001	3.17	1.48–6.80	0.003
Chronic obstructive pulmonary disease	0.24	0.13–0.43	<0.001	0.40	0.15–1.06	0.066
Chronic heart failure	7.47	4.30–12.97	<0.001	3.44	1.52–7.83	0.003
C-reactive protein (mg/L)	1.01	1.01–1.02	<0.001	1.01	1.00–1.01	<0.001
Procalcitonin (ng/mL)	1.10	1.05–1.15	<0.001	1.02	0.96–1.09	0.506
FBG $\geq$ 7.0 mmol/L	3.07	2.06–4.57	<0.001	2.20	1.21–4.03	0.010

HR, hazard ratio; CI, confidence interval; FBG, fasting blood glucose.

showed FBG associated with mortality rate in COVID-19 patients with diabetes [14]. Notably, the present study found that, not only among known diabetes patients, but also in all the in-hospital COVID-19 patients, FBG $\geq$ 7.0 mmol/L was an independent risk factor of mortality in patients with COVID-19. Specifically, in patients without diabetes history, the death rate was elevated significantly in response to hyperglycemia. The reasons why hyperglycemia but not diabetes history serves as an independent factor of death rate in COVID-19 patients appear to be due to not only the mecha-

nisms concerning the effects of hyperglycemia on inflammation and angiotensin-converting enzyme 2 (ACE2) expression, but also the effects of diabetes-associated multifactorial factors on contributing to death in COVID-19 patients. For instance, patients with diabetes and COVID-19 were older, and had more severe inflammation and comorbidities, including hypertension, coronary heart disease, chronic renal failure and chronic heart failure, which also affected the mortality rate of COVID-19. Given this, it is very likely that the role of diabetes history as an independent risk factor for the mor-

tality of COVID-19 was superimposed by other factors. In addition, dissociation of hyperglycemia from diabetes history likely also negated the role of diabetes as an independent factor for death rate in COVID-19 patients. As supporting evidence, certain patients without diabetes history had developed acute stress hyperglycemia after infection of COVID-19 [15]. Our findings indicated that screening FBG level is an effective and simple method to evaluate the prognosis of patients with COVID-19, and intervention should be taken in time when patients with FBG $\geq$ 7.0 mmol/L regardless of the presence or not of a history of diabetes.

We did not analyze the exact relationship between hypoglycemia and mortality due to the patients with FBG < 3.9 m mol/L were rare in the present study. Actually, in both diabetes and non-diabetes groups, the death rates were high at a lower level of FBG. It was worth noting that patients with hypoglycemia were very old, and probably had a few comorbidities. It demonstrated that hypoglycemia appeared to reflect a poor general health condition, rather than a direct cause of death [16].

There are some mechanisms that FBG $\geq$ 7.0 mmol/L might play a role in COVID-19 infection and poor prognosis. Since immunity is the first line of defense against SARS-CoV-2, it appears that the disturbed immunity in patients with hyperglycemia allowed unhindered proliferation of the pathogen within the host [17]. Hyperglycemia inhibits neutrophil chemotaxis, decreases phagocytosis by neutrophils, macrophages, and monocytes, and impairs innate cell-mediated immunity [18]. In patients with COVID-19, the proportion of proinflammatory Th17 CD4 + T cells and cytokine levels were elevated whereas peripheral counts of CD4 + and CD8 + T cells were decreased [19]. As such, patients with hyperglycemia may display impaired anti-viral IFN responses and delayed activation of Th1/Th17, which contributed to hyperinflammatory response [19]. On the other hand, it has been reported that elevated blood glucose levels could directly increase glucose concentrations in airway secretion, which may undermine the defensive ability of airway epithelia [20]. Consistently, in the present study, the proportion of lymphocytes was declined and the CRP levels were increased in patients with diabetes. As substantial evidence, we revealed that the CRP level was a risk factor of the mortality in COVID-19. Moreover, CRP and PCT levels were elevated more significantly in patients with diabetes who developed COVID-19. The study by Guo et al also revealed that the serum levels of inflammation-related biomarkers such as IL-6 and CRP were significantly higher in COVID-19 patients with diabetes [8]. Accumulating evidence suggests that patients with severe COVID-19 have increased incidence of a cytokine storm syndrome, which would cause mortality [6,21]. Due to exaggerated inflammatory responses, patients with hyperglycemia were more susceptible to cytokine storm, which appeared to lead to rapid deterioration of COVID-19.

As the cellular receptor for SARS-CoV-2 [22] ACE2 may also account for the association between diabetes and COVID-19. ACE2 is abundant in the type I and II alveolar epithelial cells, endothelial cells, kidney tubular epithelium, heart and pancreas [19]. Latest study confirmed human pancreatic beta cells are highly permissive to SARS-CoV-2 infection [23]. Furthermore, patients with diabetes were often treated with

the pioglitazone and liraglutide to control glucose levels, which could upregulate ACE2 levels and facilitate SARS-CoV-2 uptake [24,25]. This may explain, in part, increased risk of severe infection in patients with hyperglycemia. In addition, the clearance of SARS-CoV-2 was delayed in patients with hyperglycemia [26]. Because of this, it is plausible that patients with hyperglycemia are susceptible to SARS-CoV-2 infection.

Although this study included a large number of patients, some limitations existed. Firstly, because of the logistical restriction at the onset of these emerging infections in Wuhan, some data were lacking from clinical examinations of patients in isolation ward or ICU, such as glycosylated hemoglobin levels and records of monitoring blood glucose during in-patients. Secondly, diabetes was not subtyped when patients admitted to hospital, and this may make the results less comprehensive. Finally, the number of COVID-19 infection worldwide is increasing rapidly, the current sample is relative small, and it is only a single center study. In order to avoid statistical bias, data from larger populations and multiple centers are warranted to further confirm the results of the present study.

Although diabetes history was associated with the mortality of patients hospitalized with COVID-19, FBG $\geq$ 7.0 mmol/l was an independent risk factor for the death of COVID-19. Our findings presented here highlight the role for FBG screening and glycemic control in COVID-19 management regardless of the presence or not of a history of diabetes.

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.

Acknowledgments

Author Contributions

Yuli Cai, Shaobo Shi, Zhongyuan Wen contributed to the conception of the work. Yuli Cai, Shaobo Shi, Fan Yang, Bo Yi, Xiaolin Chen, Junfeng Li contributed to the data collection. Yuli Cai, Shaobo Shi, Fan Yang contributed to the data analysis. Yuli Cai, Shaobo Shi, Zhongyuan Wen drafted the article. All authors contributed to the interpretation of data and critical revision of the Article. All authors gave final approval of the version to be published.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108437.

REFERENCES

[1] Zhu Na, Zhang D, Wang W, Li X, Yang Bo, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33.

[2] Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JCN. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23(6):623–8.

[3] Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. International Journal of Infectious Diseases 2016;49:129–33.

[4] Guan W-J, Ni Z-y, Hu Yu, Liang W-H, Ou C-Q, He J-X, Liu L, Shan H, Lei C-L, Hui DSC, Du B, Li L-J, Zeng G, Yuen K-Y, Chen R-C, Tang C-l, Wang T, Chen P-Y, Xiang J, Li S-Y, Wang J-L, Liang Z-J, Peng Y-X, Wei Li, Liu Y, Hu Y-H, Peng P, Wang J-M, Liu J-Y, Chen Z, Li G, Zheng Z-J, Qiu S-Q, Luo J, Ye C-J, Zhu S-Y, Zhong N-S. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382(18):1708–20.

[5] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Yi, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395(10229):1054–62.

[6] Wang D, Hu Bo, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020;323(11):1061. https://doi.org/10.1001/jama.2020.1585.

[7] Shi S, Qin Mu, Shen Bo, Cai Y, Liu T, Yang F, Gong W, Liu Xu, Liang J, Zhao Q, Huang He, Yang Bo, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol 2020;5(7):802. https://doi.org/10.1001/jamacardio.2020.0950.

[8] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020:e3319. doi:10.1002/dmrr.3319.

[9] Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X, Dong K. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diab Res Care 2020;8(1): e001343. https://doi.org/10.1136/bmjdrc-2020-001343.

[10] Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526–33. https://doi.org/10.1001/jama.2012.5669.

[11] Stevens PE, Levin A, Disease K. Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158 (11):825–30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007.

[12] Wang M, Wu Q, Xu W, Qiao B, Wang J, Zheng H et al. Clinical diagnosis of 8274 samples with 2019-novel coronavirus in Wuhan. medRxiv preprint doi: https://doi.org/10.1101/2020.02.12.20022327.

[13] Zhu L, She Z-G, Cheng Xu, Qin J-J, Zhang X-J, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen Xi, Xiang M, Zhang C, Bai L, Xiang Da, Chen M-M, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang C, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang B-H, Li H. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020;31 (6):1068–1077.e3.

[14] Kong W, Zhang J, Xu Y, Li Li, Li Q, Yang Li, Wang H, Hu Yu, Chen L, Pan An, Zeng T. Letter to the Editor: Fasting plasma glucose associated with mortality rate in T2DM patients with COVID-19 infection. Metabolism 2020;108:154255. https://doi.org/10.1016/j.metabol.2020.154255.

[15] Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47(3):193–9.

[16] Majumdar SR, Hemmelgarn BR, Lin M, McBrien K, Manns BJ, Tonelli M. Hypoglycemia Associated With Hospitalization and Adverse Events in Older People: Population-based cohort study. Diabetes Care 2013;36(11):3585–90.

[17] Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: The conundrum. Diabetes Res Clin Pract 2020;162:108132. https://doi.org/10.1016/j.diabres.2020.108132.

[18] Ma RCW, Holt RIG. COVID-19 and diabetes. Diabet. Med. 2020;37(5):723–5.

[19] Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. American Journal of Physiology-Endocrinology and Metabolism 2020;318(5):E736–41.

[20] Philips BJ, Meguer J-X, Redman J, Baker EH. Factors determining the appearance of glucose in upper and lower respiratory tract secretions. Intensive Care Med 2003;29 (12):2204–10.

[21] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang Li. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020;395(10223):507–13.

[22] Yan R, Zhang Y, Li Y, Xia Lu, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367(6485):1444–8.

[23] Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X et al. A Human Pluripotent Stem Cell-based Platform to Study SARS-CoV-2 Tropism and Model Virus Infection in Human Cells and Organoids. Cell Stem Cell. 2020;In Press.

[24] Romani-Perez M, Outeirino-Iglesias V, Moya CM, Santisteban P, Gonzalez-Matias LC, Vigo E et al. Activation of the GLP-1 Receptor by Liraglutide Increases ACE2 Expression, Reversing Right Ventricle Hypertrophy, and Improving the Production of SP-A and SP-B in the Lungs of Type 1 Diabetes Rats. Endocrinology. 2015;156(10):3559-69. doi:10.1210/en.2014-1685.

[25] Zhang W, Xu Y-Z, Liu Bo, Wu R, Yang Y-Y, Xiao X-Q, Zhang X. Pioglitazone Upregulates Angiotensin Converting Enzyme 2 Expression in Insulin-Sensitive Tissues in Rats with High-Fat Diet-Induced Nonalcoholic Steatohepatitis. The Scientific World Journal 2014;2014:1–7.

[26] Chen X, Hu W, Ling J, Mo P, Zhang Y, Jiang Q et al. Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. medRxiv preprint doi: https://doi.org/10.1101/2020.03.22.20040774.