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Risk factors associated with the progression of COVID-19 in elderly diabetes patients



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ABSTRACT

Aim: To describe the clinical characteristics and risk factors associated with the progression of COVID-19 in elderly diabetes patients.

Methods: This was a retrospective cohort study, including elderly COVID-19 patients admitted to Wuhan Huoshenshan Hospital between February 10 and 13, 2020. Demographic data, medical history, signs and symptoms, and laboratory parameters were collected and analysed.

Results: We included 131 elderly COVID-19 patients (50 patients with diabetes). COVID-19 diabetes patients experienced more severe pneumonia and abnormal organ functions than non-diabetes patients ($P < 0.05$ or $P < 0.01$). Most function indicators were significantly different between the mild to moderate and severely ill groups in diabetes patients ($P < 0.05$ or $P < 0.01$). Python analysis confirmed diabetes was the independent risk factor of COVID-19 progression in elderly patients. All blood glucose (BG) indices went into the risk factor equation. The cut-off values of COVID-19 progression were BG value on admission > 8.0 mmol/L or maximum BG value > 12.0 mmol/L in all elderly patients, and BG value on admission > 5.1 mmol/L or maximum BG value > 5.4 mmol/L in non-diabetes patients.

Conclusions: Diabetes is an independent important risk factor, and glucose levels associate closely with COVID-19 progression in elderly patients.

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Abbreviations: COVID-19, coronavirus disease 2019; MERS, Middle East respiratory syndrome; CHD, coronary atherosclerotic heart disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; RNA, ribonucleic acid; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; MODS, multiple-organ dysfunction syndrome; BG, blood glucose; T2DM, type 2 diabetes mellitus; cTNI, cardiac troponin I; cTNT, cardiac troponin T; ULN, upper limit of normal; MRI, magnetic resonance imaging; IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein; BNP, brain natriuretic peptide; PT, prothrombin time; APPT, activated partial thromboplastin time; OR, odds ratio

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1. Introduction

In December 2019, a cluster of cases with pneumonia caused by a novel RNA beta-coronavirus (SARS-CoV-2) emerged. The World Health Organization (WHO) named it coronavirus disease 2019 (COVID-19) and declared it a pandemic recently. Severe cases of COVID-19 can rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS) [1].

It has previously been observed that patients with older age and chronic underlying conditions might have a considerable risk of experiencing severe cases and higher mortality [1–4]. Moreover, recent evidence suggested that diabetes might be a risk factor for the progression and prognosis of COVID-19 [5,6]. Patients with diabetes are more susceptible to infections and exhibit worse prognosis than patients without diabetes [7], which is believed to be due to the detrimental effects of hyperglycaemia to control viremia and inflammation [8]. Data from several studies showed that diabetes has become one of the most common comorbidities in infected individuals [2,9]. As the COVID-19 pandemic progresses, the high incidence of diabetes worldwide makes this problem particularly worrying. Previous clinical trials examining the effects of glucose control on mortality have controversial results [8]. Despite the multiple epidemiological studies regarding COVID-19 in patients with diabetes, the risk factors for COVID-19 in elderly patients with diabetes have not been well described. In elderly individuals with COVID-19 and pre-existing type 2 diabetes mellitus (T2DM), a key challenge for clinicians is to improve outcomes in the face of uncertainty regarding the degree of glycaemic management that should be maintained and its benefits and risks.

To our knowledge, no previous studies have been performed to estimate the risk factors for severe disease in elderly COVID-19 diabetes patients. Therefore, in this study, we aim to report the clinical characteristics and risk factors associated with the progression of COVID-19 in elderly diabetes patients.

2. Materials and methods

2.1. Study design and participants

This was a single-centred, retrospective cohort study, and the study protocol was approved by the Institutional Ethics Committee of Huoshenshan Hospital (HSSL030). Given the urgency of the COVID-19 pandemic, the need for informed consent forms were waived by the ethics board of the hospitals.

The study screened all patients with COVID-19 from two regular wards and one intensive care unit (ICU) hospitalised in Wuhan Huoshenshan Hospital between February 10 and 13, 2020. COVID-19 was diagnosed based on chest computed tomography (CT) manifestations and/or reverse transcription-polymerase chain reaction (RT-PCR) following the criteria of the New Coronavirus Pneumonia Prevention and Control Program (fifth and sixth edition at that time,

National Health Commission of China, 2020; World Health Organization, 2020) [10,11].

2.2. Data collection

Collected data including demographic data, medical history, signs and symptoms, laboratory parameters, CT scans, and outcomes were extracted from electronic medical records. The outcomes were followed up until March 04, 2020. The patients' medical records were analysed by an integrated research team, including physicians, data scientists, and statisticians. After the deidentification process of removing the participants' personal information (e.g. name and ID) and using a coding system, the data were analysed.

2.3. Definitions

The COVID-19 diagnostic criteria of the New Coronavirus Pneumonia Prevention and Control Program were as follows: (1) fever and/or other typical respiratory symptoms, (2) typical CT image manifestations of viral pneumonia, and (3) a positive RT-PCR result for COVID-19 RNA and/or gene diagnosis. Criteria for severe COVID-19 patients were as follows: (1) respiratory distress, with respiratory rate ≥ 30 breaths/min, (2) finger oxygen saturation $\leq 93\%$ in the resting state, and (3) arterial blood oxygen partial pressure (PaO₂/oxygen concentration (FiO₂) ≤ 300 mmHg.

The T2DM status was designated based on the patient's medical history and guideline for the prevention and control of T2DM in China (2017) (Chinese Diabetes Society, 2018). The timing and frequency of obtaining the fasting and 2-h postprandial blood glucose (BG) (2-hPG) varied between individuals, depending on the necessity related to the severity of the comorbid T2DM.

Hypertension, cardiac injury, acute liver injury, and acute kidney injury status were designated based on the patient's medical history and guideline for diagnosis [12]. Cardiac injury was defined when the serum levels of the cardiac injury biomarkers cardiac troponin I (cTNI) and cardiac troponin T (cTNT) were higher than the upper limit of normal (ULN). Acute liver injury was defined when an acutely increased level of serum alanine aminotransferase (ALT) and serum alkaline phosphatase of ULN was observed [13]. Acute kidney injury was indicated by the value of serum creatinine level when it exceeded the ULN ($\mu\text{mmol/L}$).

2.4. Statistical analysis

All statistical analyses were performed using SPSS Statistics (version 23.0, IBM, Armonk, NY, USA) and Python 3.6 (Python Software Foundation, Delaware, USA). Data with continuous variables were presented as mean \pm SD or median (interquartile range [IQR]), and data with categorical variables were presented as frequency rates and percentage (%). Comparison between two groups was analysed using Student's t-tests (normally distributed) or Mann-Whitney U test (non-normally distributed) for continuous variables. Comparison

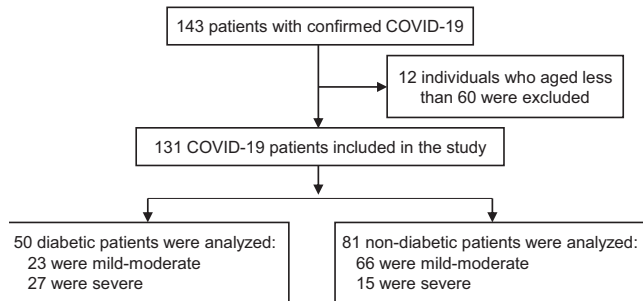


Fig. 1 – Diagram of study inclusion criteria.

of categorical variables was analysed by Fisher's exact test or χ^2 test. The risk and corresponding hazard ratio (HR) for severe condition were analysed using Python by fourfold cross-

validation. Cut-off values of BG to predict COVID-19 severity were analysed using Python by the SHAP (SHapley Additive exPlanations) method [14]. A difference with a two-tailed P value < 0.05 was considered statistically significant.

3. Results

3.1. Population

A total of 143 patients were initially screened for the study, and 12 patients younger than 60 years old were excluded. The 131 patients were divided into two groups: diabetes patients (n = 50) and non-diabetes patients (n = 81) according to the clinical diagnosis and/or medical history on admission (Fig. 1). Differences were compared between two groups, and risk factors were analysed.

Table 1 – Demographics and symptomatic characteristics of patients with COVID-19.

	Total (%) (n = 131)	Diabetes (%) (n = 50)	Non-diabetes (%) (n = 81)	P value
Age, median (IQR)	67 (62–72)	68.5 (62–75)	67 (62–71)	0.137
Gender				0.745
Male	71 (54.2)	28 (56.0)	43 (53.1)	
Female	60 (45.8)	22 (44.0)	38 (46.9)	
Diagnosis method				0.087
RT-PCR	118 (90.1)	42 (82.0)	76 (93.8)	
Gene	1 (0.8)	1 (2.0)	0 (0.0)	
Clinical diagnosis	12 (9.2)	7 (14.0)	5 (6.2)	
CT side				0.348
Unilateral	6 (4.6)	1 (2.0)	5 (6.2)	
Bilateral	122 (93.1)	47 (94.0)	75 (92.6)	
Unclear	3 (2.3)	2 (4.0)	1 (1.2)	
Comorbidities				
Diabetes	50 (38.2)	50 (100)	0 (0.0)	/
Hypertension	51 (38.9)	24 (48.0)	27 (33.3)	0.094
CHD	15 (11.5)	6 (12.0)	9 (11.1)	0.877
Cerebrovascular disease	6 (4.6)	3 (6.0)	3 (3.7)	0.417
Liver disease	3 (2.3)	1 (2.0)	2 (2.5)	0.675
Kidney disease	5 (3.8)	3 (6.0)	2 (2.5)	0.283
COPD	3 (2.3)	1 (2.0)	2 (2.5)	0.675
Malignancy	7 (5.3)	1 (2.0)	6 (7.4)	0.177
Signs and symptoms				
Fever	106 (80.9)	38 (76.0)	68 (84.0)	0.261
Cough	110 (84.0)	41 (82.0)	69 (85.2)	0.629
Expectoration	23 (17.6)	12 (24.0)	11 (13.6)	0.128
Rhinorrhoea	2 (1.5)	1 (2.0)	1 (1.5)	0.619
Haemoptysis	1 (0.8)	1 (2.0)	0 (0.0)	0.382
Shortness of breath	86 (65.6)	40 (80.0)	46 (56.8)	0.007
Fatigue	83 (63.4)	34 (68.0)	49(60.5)	0.386
Myalgia	52 (39.7)	20 (40.0)	32 (39.5)	0.955
Diarrhoea	13 (9.9)	4 (8.0)	9 (11.1)	0.781
Nausea and vomiting	12 (9.2)	7 (14.0)	5 (6.2)	0.231
Arrhythmias	9 (6.9)	8 (16.0)	1 (1.2)	0.004
Palpitation	6 (4.6)	2 (4.0)	4 (4.9)	0.583
Dizziness	5 (3.8)	2 (4.0)	3 (3.7)	0.634
Headache	4 (3.1)	2 (4.0)	2 (2.5)	0.494
Outcome				<0.001
Still in hospital	22 (16.8)	13 (26.0)	9 (11.1)	
Discharged	93 (71.0)	25 (50.0)	68 (84.0)	
Death	16 (12.2)	12 (24.0)	4 (4.9)	

Abbreviation: IQR, interquartile range; CHD, coronary atherosclerotic heart disease; COPD, chronic obstructive pulmonary diseases.

Table 2 – Laboratory parameters of patients with COVID-19.

	Reference values	Total (n = 131)	Diabetes (n = 50)	Non-diabetes (n = 81)	P value
Blood oxygen desaturation, n (%)		52 (39.7)	28 (56.0)	24 (29.6)	0.003
Blood glucose					
Maximum BG, median (IQR), mmol/L	3.9–6.11	6.34 (5.02–15.2)	17.15 (14.2–21.3)	5.11 (4.72–5.76)	<0.001
BG at the time of admission, median (IQR), mmol/L	3.9–6.11	5.27 (4.81–7.8)	8.1 (5.93–12.8)	4.92 (4.5–5.32)	<0.001
Average BG at the day of admission, median (IQR), mmol/L	3.9–6.11	5.37 (4.81–8.83)	9.91 (7.41–14.21)	4.92 (4.5–5.32)	<0.001
Biochemical detection					
Total protein, median (IQR), g/L	65–85	60.6 (57.2–65.2)	59.85 (57.1–63.6)	61.15 (57.7–66.15)	0.225
ALT, median (IQR), IU/L	7–40	25.1 (16.6–42)	24.1 (16.2–44.4)	25.3 (16.95–38.7)	0.789
AST, median (IQR), IU/L	7–45	23.4 (16.8–33.9)	26 (18.4–38)	22.3 (16.7–31.5)	0.102
Albumin, median (IQR), g/L	40–55	33.5 (30.3–36.4)	31.9 (30.1–35.5)	34.2 (30.9–36.95)	0.046
BUN, median (IQR), mmol/L	2.6–7.5	5.01 (4.05–6.9)	5.93 (4.61–8.43)	4.73 (3.83–5.89)	0.001
Creatinine, median (IQR), $\mu\text{mol/L}$	41–73	67.9 (57.6–82.6)	71.55 (61.3–82.85)	67.6 (55.6–81.75)	0.356
Uric acid, median (IQR), $\mu\text{mol/L}$	142–340	267 (192–336)	247 (182–351)	270 (205–332.5)	0.404
Total bile acid, median (IQR), $\mu\text{mol/L}$	0–10	3.7 (2.5–5.6)	4 (2.5–6.5)	3.65 (2.5–5.45)	0.445
Creatine kinase, median (IQR), IU/L	24–170	42.8 (29.3–71.3)	42.35 (27.7–75.9)	42.45 (31.05–68.73)	0.861
Creatine kinase-MB, median (IQR), IU/L	0–24	10.1 (7.4–12.7)	10.88 (8.1–12.7)	9.7 (7.3–12.8)	0.142
LDH, median (IQR), IU/L	120–250	227.6 (174.1–325)	284.1 (192.4–461.7)	201.35 (172.35–272.85)	<0.001
Troponin I, median (IQR), ng/mL	0–0.04	0.01 (0.01–0.34)	0.025 (0.01–0.046)	0.01 (0.01–0.022)	0.557
Myohaemoglobin, median (IQR), ng/mL	0–65	10.53 (5.11–33.30)	21.89 (8.23–47.67)	9.35 (3.47–14.7)	0.175
BNP, median (IQR), pg/mL	0–100	54.21 (0.28–123.08)	68.77 (13.29–123.08)	48.65 (0.01–123.08)	0.336
Inflammatory indices					
Procalcitonin, median (IQR), ng/mL	0–0.05	0.06 (0.04–0.18)	0.95 (0.05–0.24)	0.04 (0.03–0.14)	0.703
CRP, median (IQR), mg/L	0–4	9.99 (2.72–54)	36.48 (5.77–87.72)	7.12 (1.86–36.03)	0.002
Blood routine examination					
White blood cell count, median (IQR), $\times 10^9/\text{L}$	3.5–9.5	6.5 (4.9–8.1)	6.97 (5.2–9)	6 (4.2–7.4)	0.023
Neutrophil percentage, median (IQR), %	40–75	69.8 (60.1–82.2)	75.95 (65.4–87.1)	65.35 (58.15–79.05)	0.004
Lymphocyte percentage, median (IQR), %	20–50	20.2 (10.3–30.6)	14.8 (7–23.8)	24.85 (12.6–31.4)	0.006
Neutrophil count, median (IQR), $\times 10^9/\text{L}$	1.8–6.3	4.65 (2.83–6.33)	5.62 (3.53–7.72)	3.96 (2.38–5.62)	0.005
Lymphocyte count, mean \pm SD, $\times 10^9/\text{L}$	1.1–3.2	1.18 (0.73–1.59)	1.04 \pm 0.57	1.26 \pm 0.51	0.025
Monocyte count, median (IQR), $\times 10^9/\text{L}$	0.1–0.6	0.43 (0.31–0.54)	0.42 (0.3–0.54)	0.44 (0.31–0.57)	0.509
Eosinophil count, median (IQR), $\times 10^9/\text{L}$	0.02–0.52	0.06 (0.02–0.11)	0.05 (0.01–0.12)	0.06 (0.03–0.1)	0.662
Red blood cell count, median (IQR), $\times 10^9/\text{L}$	4.3–5.8	3.99 (3.7–4.33)	4.06 (3.74–4.34)	3.97 (3.64–4.28)	0.172
Haemoglobin, median (IQR), g/L	130–175	122.023 (111–132)	124 (114–136)	120.5 (109.5–131)	0.111
Platelet count, mean \pm SD, $\times 10^9/\text{L}$	125–350	259 (187–319)	220.69 \pm 100.49	269.3 \pm 79.41	0.002
Coagulation indices					
PT, median (IQR), seconds	9.2–15	13.39 (12.44–14.16)	13.95 (12.42–14.73)	13.29 (12.46–13.95)	0.136
APPT, median (IQR), seconds	21–37	28.44 (25.81–30.07)	27.93 (25.23–29.17)	28.44 (26.37–30.23)	0.198
D-dimer, median (IQR), mg/L	0–0.55	1.36 (0.52–2.57)	2.57 (0.83–3.88)	0.85 (0.43–2.57)	0.001

Abbreviation: IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, urea nitrogen; LDH, lactate dehydrogenase; BNP, brain natriuretic peptide; CRP, C-reactive protein; PT, prothrombin time; APPT, activated partial thromboplastin time.

Table 3 – Difference of mild to moderate and severely ill groups in diabetes and non-diabetes elderly patients.

	Reference values	Diabetes (n = 50)			Non-diabetes (n = 81)		
		Mild to moderate (n = 23, 46%)	Severe (n = 27, 54%)	P value	Mild to moderate (n = 66, 81.5%)	Severe (n = 15, 18.5%)	P value
Blood glucose(mmol/L)							
Maximum BG	3.9–6.11	16.7 (13.21–19.3)	17.37 (14.83–24.06)	0.169	5.03 (4.67–5.38)	7.42 (5.44–8.75)	<0.001
BG at the time of admission	3.9–6.11	7.3 (5.95–9)	9.6 (6.02–13.7)	0.088	4.86 (4.48–5.13)	5.71 (4.91–7.78)	0.018
Average BG	3.9–6.11	9 (7.42–11.99)	11.4 (7.75–14.61)	0.191	4.86 (4.48–5.13)	5.71 (4.91–7.7)	0.018
Biochemical detection							
Total protein (g/L)	65–85	61.2 (58.5–64.55)	58.4 (54–62.4)	0.025	61.85 (58.6–67)	58.6 (55.7–61.6)	0.02
ALT (IU/L)	7–40	19.9 (14.45–31.46)	36.2 (20.1–47.7)	0.067	22.45 (16.4–37.4)	34.3 (24.95–88.6)	0.02
AST (IU/L)	7–45	17.8 (15.55–28.65)	30.2 (24.8–38.6)	0.002	21.45 (15.4–27.4)	30.8 (28.92–51)	0.002
Albumin (g/L)	40–55	34.88 ± 3.8	30.68 ± 2.82	<0.001	34.7 (32.7–37.4)	30.7 (27.55–33.05)	0.001
BUN (mmol/L)	2.6–7.5	5.56 (4.17–6)	6.9 (5.5–9.64)	0.031	4.55 (3.75–5.42)	5.82 (4.87–8.39)	0.007
Creatine kinase (IU/L)	24–170	34.8 (26.65–44)	69.3 (36.1–99.8)	0.004	42.05 (31.3–67.06)	59 (26.7–118.9)	0.293
Creatine kinase-MB (IU/L)	0–24	8.8 (6.65–11.25)	11.6 (10.1–15.15)	0.003	8.9 (6.7–11.2)	13.6 (10.53–18.25)	<0.001
LDH (IU/L)	120–250	207.09 ± 58.01	461.01 ± 146.89	<0.001	190.8 (165.6–227.6)	360 (264.05–434.75)	<0.001
Inflammatory indices							
CRP (mg/L)	0–4	6.02 (3.82–34.52)	75.68 (34.42–127.67)	<0.001	4.32 (1.26–10.64)	61.71 (21.34–148.34)	<0.001
Blood routine examination							
White blood cell count (×10 ⁹ /L)	3.5–9.5	6.26 ± 1.82	8.38 ± 3.08	0.006	5.5 (4.1–6.8)	9.7 (7.15–13.3)	<0.001
Neutrophil percentage (%)	40–75	67.2 (59.05–72.85)	86.2 (79.5–92.6)	<0.001	62.5 (57.4–71.1)	88.6 (82.95–92.05)	<0.001
Lymphocyte percentage (%)	20–50	21 (16.7–31.95)	8.1 (4.2–13.45)	<0.001	27.8 (19–31.8)	6.6 (4.75–11.7)	<0.001
Neutrophil count (×10 ⁹ /L)	1.8–6.3	3.96 (2.88–5.55)	7.13 (5.55–8.4)	<0.001	3.55 (2.33–4.81)	8.83 (5.97–11.77)	<0.001
Lymphocyte count (×10 ⁹ /L)	1.1–3.2	1.41 ± 0.52	0.73 ± 0.4	<0.001	1.37 ± 0.48	0.76 ± 0.32	<0.001
Eosinophil count (×10 ⁹ /L)	0.02–0.52	0.09 (0.06–0.15)	0.02 (0–0.04)	<0.001	0.07 (0.04–0.11)	0.01 (0–0.05)	<0.001
Red blood cell count (×10 ⁹ /L)	4.3–5.8	3.93 (3.72–4.13)	4.22 (3.94–4.64)	0.029	3.94 (3.63–4.17)	4.12 (3.85–4.49)	0.173
Platelet count (×10 ⁹ /L)	125–350	265.59 ± 100.73	182.44 ± 84.51	0.003	269.5 ± 76.21	263.15 ± 97.19	0.403
Coagulation indices							
PT (seconds)	9.2–15	12.59 (12.2–13.95)	14.26 (13.9–16.73)	<0.001	13.25 (12.46–13.95)	13.95 (12.7–14.21)	0.151
D-dimer (mg/L)	0–0.55	1.17 (0.41–2.57)	2.57 (2.3–6.43)	0.002	0.69 (0.36–2.57)	2.57 (0.71–4.09)	0.004

Abbreviation: IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein; PT, prothrombin time.

3.2. General conditions of elderly participants and difference between diabetes and non-diabetes patients

Of the 131 inpatients with COVID-19, the median age was 67 (IQR, 62–72). There were 60 (45.8%) female patients; 89 were mild to moderate patients (67.9%), and 42 were severely ill patients (32.1%). All patients were scanned using chest CT. The three most common symptoms were cough (110 [84.0%]), fever (106 [80.9%]), and shortness of breath (86 [65.6%]); the less common symptoms were haemoptysis (1 [0.8%] of 131 patients), rhinorrhoea (2 [1.5%]), and headache (4 [3.1%]). The most common comorbidities were hypertension, diabetes, and coronary atherosclerotic heart disease (38.9%, 38.2%, and 11.5%) (Table 1).

There was no difference in age, gender, and diagnostic methods between diabetes and non-diabetes patients ($P > 0.05$). Among all influenza-like symptoms, respiratory symptoms, neuromuscular symptoms, and circulatory symptoms, only shortness of breath and arrhythmia had statistically significant differences between diabetes and non-diabetes patients ($P < 0.01$) (Table 1). There were 46% diabetes patients with mild to moderate symptoms and 54% with severe symptoms, compared to the 81.5% non-diabetes patients with mild to moderate symptoms and 18.5% with severe symptoms (Table 3).

3.3. Clinical laboratory differences between diabetes and non-diabetes elderly patients

Laboratory tests after admission was shown in Table 2. Of the 131 cases, a medium level of maximum BG and inflammatory indices (procalcitonin, c-reactive protein [CRP]) were higher than the normal range (Table 2).

All BG indices showed a significant difference between diabetes and non-diabetes patients ($P < 0.01$). Blood oxygen saturation was significantly lower in diabetes patients

($P < 0.01$). Albumin level, kidney function (blood urea nitrogen [BUN]), indicators of myocardial injury (lactate dehydrogenase [LDH]), inflammatory factors (CRP), and coagulation indicator (D-dimer) for biochemical detection in the diabetes groups were all inferior to the non-diabetes group ($P < 0.05$ or $P < 0.01$). All indices for blood routine examination, except monocyte count, eosinophil count, and red blood cell count, showed a significant difference between the diabetes and non-diabetes groups ($P < 0.05$ or $P < 0.01$) (Table 2).

3.4. Differences of mild to moderate and severely ill groups between diabetes and non-diabetes elderly patients

Among all the indices, nutritional indices (total protein, albumin levels), liver and kidney function tests (AST, BUN, and LDH), myocardial injury indices (creatinine kinase, creatine kinase-MB, LDH), inflammatory marker (CRP), most routine blood test indicators (white blood cell count, neutrophil count and percentage, lymphocyte count and percentage, eosinophil count, red blood cell count, and platelet count), and coagulation indicators (prothrombin time [PT], D-dimer) were expressed significantly differently between the mild to moderate and severely ill groups in diabetes patients ($P < 0.05$ or $P < 0.01$) (Table 3).

Compared with diabetes patients, all BG indices (BG value at the time of admission, maximum BG value, average BG value on the day of admission) and ALT level were significantly different between the mild to moderate and severely ill groups in non-diabetes patients ($P < 0.05$ or $P < 0.01$) (Table 3), but not in diabetes patients. Conversely, a difference in creatine kinase level, red blood cell count, and PT, as seen in diabetes patients, could not be found in the non-diabetes subgroups between the mild to moderate and severely ill groups ($P > 0.05$).

Table 4 – Python analysis of risk factors associated with severe COVID-19 progression in elderly patients.

Factors	Total			Diabetes			Non-diabetes		
	Rank	β -value	HR value	Rank	β -value	HR value	Rank	β -value	HR value
Diabetes	7	0.58	1.79						
Maximum BG	9	0.55	1.73				2	0.57	1.77
BG at the time of admission	8	0.56	1.75				8	0.32	1.38
Average BG	11	0.52	1.68				9	0.32	1.38
Systolic pressure	6	0.59	1.8						
Hypertension	10	0.53	1.7				1	0.65	1.92
CRP	1	1.14	3.12	3	0.85	2.34	3	0.56	1.76
LDH	2	1.08	2.94	1	1.08	2.95	6	0.42	1.52
D-dimer	5	0.73	2.07	5	0.6	1.81	11	0.30	1.35
Neutrophil count	3	0.89	2.42	2	0.95	2.57	5	0.52	1.68
ALT	4	0.84	2.32	9	0.2	1.22	4	0.54	1.71
AST	13	0.51	1.66	10	0.08	1.08	7	0.36	1.43
Body temperature				4	0.68	1.97			
Heart rate				6	0.46	1.59			
PT				7	0.37	1.45			
Creatine kinase	15	0.46	1.58	8	0.35	1.41			
CT description	14	0.50	1.64				10	0.3	1.35

Abbreviation: BG, blood glucose; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate

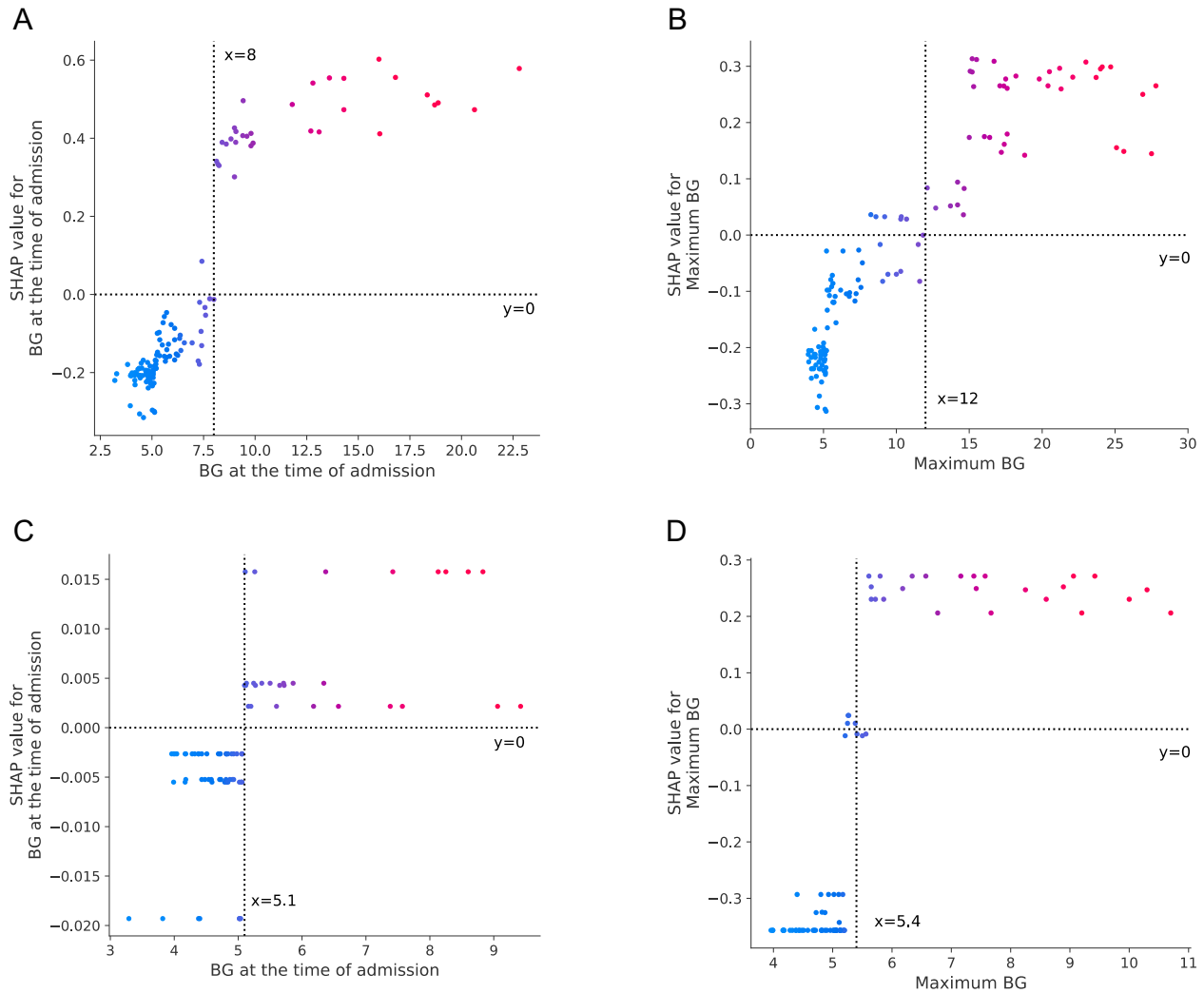


Fig. 2 – Cut-off values of blood glucose analysed by SHAP. (A–B) SHAP values for BG at the time of admission and maximum BG in all elderly COVID-19 patients; (C–D) SHAP values for BG at the time of admission and maximum BG in non-diabetes elderly COVID-19 patients. SHAP value represents the contribution of each element to the model.

3.5. Risk factors and blood glucose cut-off values associated with COVID-19 progression

All difference indicators in univariate comparison were included in the Python analysis to obtain the risk and corresponding HR. Among all indicators that showed a difference, decreased oxygen saturation, shortness of breath, and respiratory rate were excluded because they were the diagnostic clinical presentation of severely ill patients. Among the neutrophil ratio, lymphatic ratio, neutrophil value, and lymphatic value, two values were selected for presentation (Table 4).

In the total population, diabetes was an independent risk factor among the top 10 risk factors associated with COVID-19 progression (hazard ratio, HR 1.79). All glucose indices went into the risk factor equation among all the elderly patients (HR 1.38–1.77, rank 8, 9, 11). The area under the curve (AUC) of the test set reached 92.24%. Cut-off results of the SHAP analysis showed that elderly patients with BG value on admission > 8.0 mmol/L or maximum BG value > 12.0 m

mol/L experienced dramatically higher trends of severity (Fig. 2 A–B).

In patients with diabetes, neutrophil count and LDH, CRP, D-dimer, ALT, and AST levels became one of the top 10 risk factors (HR 1.81–2.95), which also became the top factors in the overall and/or non-diabetes population. Body temperature, heart rate, PT, and creatine kinase level solely became the top influential factors of progression in diabetes patients (HR 1.08–1.59). Hypertension was not included in the top factors affecting diabetes patients.

Furthermore, in non-diabetes elderly patients, all glucose indices went into the risk factor equation (HR 1.38–1.77, rank 2, 8, 9). BG value on admission > 5.1 mmol/L or maximum BG value > 5.4 mmol/L was the cut-off value for COVID-19 progression (Fig. 2 C–D).

4. Discussion

In this study, we reported the clinical characteristics of elderly COVID-19 patients. The most frequent comorbidities were

hypertension, diabetes, and cardiovascular diseases, similar to the previously reported results [2,15,16]. However, in the present cohort, patients with diabetes reached 38.2% (50 of 131), and 32.1% patients were severe cases, which were higher than other studies [5,15,17]. Furthermore, 75% of deceased cases had diabetes, which was higher than that in survivors (26.9%). The reasons might be that Huoshenshan Hospital was responsible for receiving diagnosed patients and prefers to treat severely ill patients, and all enrolled individuals were aged over 60 years. There was no obvious demographic and symptomatic difference between diabetes and non-diabetes patients.

Univariable and regression analyses were performed to compare laboratory parameters in the diabetes and non-diabetes groups and mild to moderate and severely ill subgroups. There were three collections of results: (1) Factors that showed a difference in all three comparisons might be the influential factors in the progression of COVID-19 in all patients. Some factors were different between diabetes and non-diabetes patients, such as blood cell counts and albumin, BUN, LDH, CRP, and D-dimer levels, while others are not, like ALT, AST, and CK-Mb (Creatine kinase – MB) levels. (2) Factors that influenced non-diabetes patients, with difference between the diabetes and non-diabetes groups, were the influential factors that diabetes patients have specifically or at a significantly higher level, like all BG indices. (3) Factors that showed a difference only in the diabetes subgroup obviously changed in diabetes patients and led to a severe condition (PT and CK; PLT also displayed the same result but was not included in the influential factors).

From the univariable and regression analyses, it could be confirmed notably that diabetes diagnosis is an independent risk factor for COVID-19 progression in elderly patients. Diabetes patients had 79% higher risk than non-diabetes patients to develop into severe cases. This finding is in accordance with other researches with its highlights [5,24]. It is known that diabetes patients are more susceptible to infectious diseases and tend to experience faster progression and worse prognosis [18–20]. Concurrently, a dysregulated immune response caused by diabetes is likely also responsible for the increased disease severity of COVID-19 in patients with diabetes [21]. The SHAP analysis revealed that elevated BG value on admission (>8.0 mmol/L) or maximum BG value (>12.0 mmol/L) was associated with poor progression in elderly COVID-19 patients. These values were consistent with the diagnostic criteria of diabetes. The SHAP analysis result is a brand-new support evidence for diabetes as an independent risk factor in COVID-19 patients. At the same time, these results also suggest that in COVID-19 patients with a history of diabetes, the glycaemic control targets might be slightly extended compared with the conventional control target [22].

Our research reveals a new interesting effect of glucose levels in elderly COVID-19 patients: BG levels are also an important risk factor for progression in non-diabetes patients. BG levels at the time of admission are independent risk factors, which means the former pancreatic status or glucose metabolic abilities relate closely with the progression of COVID-19, even if they do not have diabetes (BG value on admission > 5.1 mmol/L is associated with poor progression). Maximum BG value is an independent risk factor in non-

diabetes patients with the highest HR. The population with a maximum BG value > 5.4 mmol/L showed a higher risk of worse progression. This may be because the maximum BG value presents the worst pancreatic conditions. It is partly consistent with a former study reporting that a well-controlled BG level could reduce adverse outcomes and death in COVID-19 patients [23]. Yang et al. studied COVID-19 patients without a history of diabetes and reported that BG level is representative of the clustered indicators of multi-organ injury and an earlier predictor of poor outcomes and death in COVID-19 patients [24–27]. As reported, elevation of glucose level may be caused by “stress hyperglycaemia” during acute illness in patients with COVID-19 and relates to both insulin secretion dysfunction and insulin resistance [22]. The concentration of BG in airway epithelial secretion would increase as BG level increased, which might break the defensiveness of the epithelia [28].

There were several other prognostic factors in elderly COVID-19 patients with diabetes that is worthy of emphasis. (1) LDH is an enzyme, existing in the myocardia, which is released into the blood when the heart is injured. It became the most effective factor in the progression of COVID-19 diabetes patients in this cohort out of our expectation. This result might be due to the high prevalence of heart injury in severe COVID-19 patients. (2) D-dimer level was also included in the top rank due to its association with COVID-19 progression in overall and diabetes patients, but not in non-diabetes patients. D-dimer level is an accepted risk factor [23], while PT is not mentioned in former studies. Further attention should be paid to disordered coagulation in diabetes patients to prevent COVID-19 progression [29]. (3) Inflammatory factors, CRP level, and neutrophil count were associated with cytokine storms caused by virus invasion, which may be related to the death of COVID-19 patients [15,21,23]. (4) Hypertension also showed a significant effect on the overall population and non-diabetes patients (the first ranking risk factor), but not in diabetes patients (there was no difference between mild to moderate and severely ill diabetes patients). The effect of hypertension might be an interesting research point in elderly COVID-19 patients. (5) Age was not included in the top 10 risk factors in neither group analysis, which might be because patients were all elderly, and the age span was only 12 years.

Our study has some limitations. First, owing to the small sample size, more clinical trials are needed to validate the findings. Second, due to the retrospective study design, not all laboratory tests were done in all patients, including those for insulin, C-peptide, HbA1c, and IL-6 levels. Therefore, their roles in predicting disease progression might be underestimated. Third, some patients were transferred from other hospitals at a later period, so the results might be different with researches where patients were included at their first visit. Fourth, we were not able to retrieve the pre-hospital status of diabetes patients from the current cohort due to the urgent circumstance of the COVID-19 pandemic.

5. Conclusions

In conclusion, diabetes is an important independent risk factor for COVID-19 progression in elderly individuals. BG indices are important predictive factors for disease severity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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WM responded to the care of the patient. WM, LW, and YG were involved in the diagnosis, management, and treatment. WM and LW collected the data. PZ, YW, and TL explained the data. YG, JZ and CL designed the study. JZ and YW conducted the analysis. JZ and TL reviewed the relevant papers. YG, PZ, and CL wrote the first draft. All authors contributed equally to writing the manuscript.

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