Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study

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OBJECTIVE

Diabetes is common in COVID-19 patients and associated with unfavorable outcomes. We aimed to describe the characteristics and outcomes and to analyze the risk factors for in-hospital mortality of COVID-19 patients with diabetes.

RESEARCH DESIGN AND METHODS

This two-center retrospective study was performed at two tertiary hospitals in Wuhan, China. Confirmed COVID-19 patients with diabetes ($N = 153$) who were discharged or died from 1 January 2020 to 8 March 2020 were identified. One sex- and age-matched COVID-19 patient without diabetes was randomly selected for each patient with diabetes. Demographic, clinical, and laboratory data were abstracted. Cox proportional hazards regression analyses were performed to identify the risk factors associated with the mortality in these patients.

RESULTS

Of 1,561 COVID-19 patients, 153 (9.8%) had diabetes, with a median age of 64.0 (interquartile range 56.0–72.0) years. A higher proportion of intensive care unit admission (17.6% vs. 7.8%, $P = 0.01$) and more fatal cases (20.3% vs. 10.5%, $P = 0.017$) were identified in COVID-19 patients with diabetes than in the matched patients. Multivariable Cox regression analyses of these 306 patients showed that hypertension (hazard ratio [HR] 2.50, 95% CI 1.30–4.78), cardiovascular disease (HR 2.24, 95% CI 1.19–4.23), and chronic pulmonary disease (HR 2.51, 95% CI 1.07–5.90) were independently associated with in-hospital death. Diabetes (HR 1.58, 95% CI 0.84–2.99) was not statistically significantly associated with in-hospital death after adjustment. Among patients with diabetes, nonsurvivors were older (76.0 vs. 63.0 years), most were male (71.0% vs. 29.0%), and they were more likely to have underlying hypertension (83.9% vs. 50.0%) and cardiovascular disease (45.2% vs. 14.8%) (all P values <0.05). Age ≥70 years (HR 2.39, 95% CI 1.03–5.56) and hypertension (HR 3.10, 95% CI 1.14–8.44) were independent risk factors for in-hospital death of patients with diabetes.

CONCLUSIONS

COVID-19 patients with diabetes had worse outcomes compared with the sex- and age-matched patients without diabetes. Older age and comorbid hypertension independently contributed to in-hospital death of patients with diabetes.

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In December 2019, pneumonia of an unknown cause was detected in Wuhan, China, which was later named coronavirus disease 2019 (COVID-19) by the World Health Organization. The virus that caused this epidemic was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak of COVID-19 swept across China and other countries, arousing global concern. As of 24 April 2020, a total of 2,626,321 COVID-19 cases were confirmed worldwide, and 181,938 patients had died (1). Compared with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), COVID-19 has a lower mortality among confirmed cases. However, elderly patients with underlying comorbidities, including diabetes, hypertension, and coronary heart disease, are at greater risk of poor outcomes (2,3).

Diabetes is one of the leading causes of morbidity, and it causes enormous health and financial burdens worldwide (4). Connections between diabetes and increased susceptibility to infections, including respiratory tract, urinary tract, and soft-tissue infections, have long been accepted (5). The available evidence demonstrates that diabetes predisposes people to developing infectious diseases, and patients with diabetes are at greater risk of infection-related mortality (6,7). Furthermore, diabetes has been associated with a poor prognosis and increased pneumonia-associated mortality (8,9). Previous studies demonstrated that diabetes is one of the major comorbidities in COVID-19 patients. Wang et al. (10) and Guan et al. (11) reported that patients with diabetes accounted for 10.1% and 7.4% of COVID-19 patients, respectively. Recent publications showed that 20–30% of nonsurviving COVID-19 patients had underlying diabetes (3,12). This evidence indicates that COVID-19 patients with diabetes might be at a higher risk of death. Thus, the clinical characteristics and risk factors for in-hospital mortality of COVID-19 patients with diabetes need to be explored.

In this study, we aimed to describe the demographic features, clinical data, treatments, and outcomes of COVID-19 patients with diabetes. We also compared the characteristics and risk factors for in-hospital death of the patients who had diabetes with those of age- and sex-matched patients without diabetes.

RESEARCH DESIGN AND METHODS

Study Design

This two-center, retrospective study was conducted at Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University, which are two major tertiary hospitals in Wuhan that serve as government-designated hospitals for the treatment of COVID-19. All the confirmed COVID-19 patients with diabetes who were discharged or died from 1 January 2020 to 8 March 2020 were identified. The patients with diabetes included in our study had a clear diagnosis of diabetes by their physicians on the electronic medical records. The age of those with diabetes (64.0 [interquartile range [IQR], 56.0–72.0] years) in our study was significantly different from the overall COVID-19 population (47.0 [IQR, 35.0–58.0] years) in China (11). Older age and male sex have also been demonstrated to be associated with in-hospital death of COVID-19 patients (3,12). Thus, to adjust age and sex, an age- (±2 years) and sex-matched COVID-19 patient without diabetes was randomly selected for each patient with diabetes according to previously reported similar methods (13,14). Whenever more than one patient was available for each patient with diabetes, the match was randomly selected from those available. This study was approved by the Institutional Ethics Boards of Renmin Hospital of Wuhan University (No. WDRY2020-K060) and Zhongnan Hospital of Wuhan University (No. 2020020), Wuhan, China. The ethic committees in these two hospitals waived informed consent. Oral consent was obtained when we contacted patients or their families for information about patients' diabetes history.

Data Abstraction

Data abstracted included age, sex, exposure history, history of diabetes, other underlying comorbidities (hypertension, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, and malignancy), onset of symptoms (fever, cough, dyspnea, myalgia, etc.), vital signs at admission (heart rate, respiratory rate, and mean artery pressure), laboratory parameters on admission (blood glucose level, white blood cell count, lymphocyte count, procalcitonin, triglyceride, etc.), random blood glucose (RBG), chest computed tomographic (CT) scans, complications (acute respiratory distress syndrome [ARDS], acute cardiac injury, acute kidney injury [AKI], shock, and secondary infections), medications for treatment (antiviral, antibacterial agents, corticosteroids, Ig), treatment strategies (supplemental oxygen, noninvasive mechanical ventilation, invasive mechanical ventilation, continuous renal replacement therapy [CRRT], and extracorporeal membrane oxygenation [ECMO]), and date of discharge or death. Duration from the onset of symptoms to admission, diagnosis of COVID-19, and total hospital length of stay were also recorded. Data were abstracted using the electronic medical record systems in Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University. All data were reviewed by a team of experienced physicians. Any uncertain or missing records were addressed through communication with the involved health care providers, the patients, or their families. Also included in our study were 14 patients with diabetes and 9 patients without diabetes in a previous publication (10).

Definitions

The diagnosis of COVID-19 was performed according to the World Health Organization interim guidance (15). The method of detection of SARS-CoV-2 using throat swabs and RT-PCR was reported previously (10). Diabetes was defined according to the guidelines of American Diabetes Association (16). Pregnant women with gestational diabetes or patients with glucocorticoid-induced hyperglycemia were identified and excluded from this study. ARDS was defined according to the Berlin definition (17). Cardiac injury was reported if serum levels of myocardial injury biomarkers (e.g., ultrasensitive troponin I) were >99th percentile of the upper reference. AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes definition (18). Shock was defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock (19). Secondary infections were diagnosed when positive cultures of pathogens were obtained from lower respiratory tract specimens or blood samples after admission (3). The calculation of average RBG was based on all the available RBG test results of the patients during this hospitalization. Average RBG = $(RBG_1 + RBG_2 + RBG_3 ... + RBGn)/n$.

Table 1—Characteristics, laboratory findings, complications, treatments, and outcomes of COVID-19 patients with diabetes and sex- and age-matched patients without diabetes

		Patients without diabetes (n = 153)	Patients with diabetes (n = 153)	P value
Age, years		65.0 (56.0–72.0)	64.0 (56.0–72.0)	0.872
Sex				1.000
Female		78 (51.0)	78 (51.0)	–
Male		75 (49.0)	75 (49.0)	–
Exposure history		31 (20.3)	18 (11.8)	**0.043**
Smoking		9 (5.9)	7 (4.6)	0.608
Drinking		7 (4.6)	6 (3.9)	0.777
Comorbidities				
Hypertension		44 (28.8)	87 (56.9)	**<0.001**
Cardiovascular disease		17 (11.1)	32 (20.9)	**0.019**
Cerebrovascular disease		2 (1.3)	12 (7.8)	**0.006**
Chronic pulmonary disease		13 (8.5)	8 (5.2)	0.258
Chronic kidney disease		6 (3.9)	6 (3.9)	1.000
Chronic liver disease		4 (2.6)	5 (3.3)	1.000
Malignancy		6 (3.9)	8 (5.2)	0.584
Signs and symptoms				
Fever		118 (77.1)	120 (78.4)	0.783
Cough		78 (51.0)	95 (62.1)	0.050
Dyspnea		60 (39.2)	52 (34.0)	0.342
Myalgia		16 (10.5)	22 (14.4)	0.298
Headache		6 (3.9)	3 (2.0)	0.501
Diarrhea		23 (15.0)	18 (11.8)	0.401
Nausea or vomiting		5 (3.3)	8 (5.2)	0.395
Anorexia		82 (53.6)	81 (52.9)	0.909
Fatigue		79 (51.6)	95 (62.1)	0.065
From onset symptom to, days				
Hospital admission		10.0 (7.0–15.0)	11.0 (7.0–18.0)	0.693
Confirmation of SARS-CoV-2		8.0 (5.0–12.0)	8.0 (4.0–14.0)	0.963
Hospital length of stay, days		15.0 (9.0–22.0)	15.0 (8.0–22.0)	0.507
ICU admission		12 (7.8)	27 (17.6)	**0.010**
Respiratory rate, rpm		20.0 (18.0–21.0)	20.0 (18.0–21.0)	0.719
Heart rate, bpm		84.0 (76.0–92.0)	83.0 (78.0–92.0)	0.665
Mean arterial pressure, mmHg		95.0 (87.0–103.0)	94.0 (87.0–102.0)	0.445
CT manifestations, area of lung injury				
<25%		81/118 (68.6)	74/121 (61.2)	0.225
25–50%		19/118 (16.1)	21/121 (17.4)	0.795
50–75%		10/118 (8.5)	19/121 (15.7)	0.087
>75%		6/118 (5.1)	8/121 (6.6)	0.615
Laboratory findings on admission	Normal range			
White blood cell count, $\times 10^9$/L	3.5–9.5	5.9 (4.1–7.5)	5.6 (4.5–8.0)	0.514
Neutrophil count, $\times 10^9$/L	1.8–6.3	3.6 (2.5–5.4)	3.8 (2.8–6.3)	0.193
Lymphocyte count, $\times 10^9$/L	1.1–3.2	1.1 (0.8–1.5)	1.0 (0.7–1.5)	0.189
Platelet count, $\times 10^9$/L	125–350	217.0 (164.0–278.0)	193.0 (141.0–267.0)	0.052
C-reactive protein, mg/L	0–10	16.8 (5.0–62.8)	23.3 (5.0–85.2)	0.178
Prothrombin time, s	9–13	12.0 (11.4–12.7)	12.0 (11.5–13.1)	0.328
D-dimer, ng/mL	0–550	570.0 (270.0–1,540.0)	683.5 (270.0–2,344.0)	0.551
ALT, units/L	9–50	22.5 (16.0–38.3)	25.0 (16.0–40.0)	0.888
Creatinine, μmol/L	57–111	62.1 (51.8–77.5)	65.2 (52.1–84.0)	0.276
eGFR, mL/min	>90	94.6 (82.8–106.6)	93.6 (74.5–104.2)	0.163
Total cholesterol, mmol/L	<5.2	4.1 (3.4–4.9)	3.8 (3.2–4.3)	**0.006**
Triglyceride, mmol/L	<1.70	1.25 (1.01–1.67)	1.37 (1.06–1.73)	0.223
pH	7.35–7.45	7.41 (7.37–7.43)	7.41 (7.36–7.45)	0.549
Pao_2, mmHg	80–100	88.0 (69.3–113.0)	68.5 (48.5–90.8)	**0.011**
Spo_2, %	95–100	97.0 (94.0–99.0)	96.0 (90.0–98.0)	0.093
Glucose, mmol/L	3.9–6.1	5.7 (4.8–7.3)	9.4 (6.9–13.3)	**<0.001**
Lactate, mmol/L	0.5–1.5	2.3 (1.6–2.8)	2.0 (1.5–2.9)	0.626
Procalcitonin, ng/mL	<0.1	0.05 (0.04–0.10)	0.06 (0.05–0.24)	**0.010**
Ultrasensitive troponin I, ng/mL	0–0.04	0.006 (0.006–0.019)	0.007 (0.006–0.034)	0.104
$CD3^+$ cell count, /μL	723–2,737	670.0 (448.0–929.0)	581.0 (307.5–1,013.5)	0.143

Continued on p. 1385

Table 1—Continued

		Patients without diabetes (n = 153)	Patients with diabetes (n = 153)	P value
$CD4^+$ cell count, /μL	404–1,612	380.0 (264.0–570.5)	365.0 (202.5–633.5)	0.517
$CD8^+$ cell count, /μL	220–1,129	242.0 (130.0–361.5)	164.0 (98.0–303.0)	**0.026**
$CD19^+$ cell count, /μL	80–616	131.0 (85.5–210.0)	143.0 (84.5–214.5)	0.610
$CD16^+56^+$ cell count, /μL	84–724	128.5 (69.8–189.3)	119.0 (72.0–201.0)	0.492
Complications				
ARDS		17 (11.1)	38 (24.8)	**0.002**
AKI		5 (3.3)	19 (12.4)	**0.003**
Acute cardiac injury		26 (17.0)	47 (30.7)	**0.005**
Shock		16 (10.5)	32 (20.9)	**0.012**
Secondary infection		17 (11.1)	37 (24.2)	**0.003**
Treatments				
Antiviral therapy		146 (95.4)	148 (96.7)	0.556
Antibiotic therapy		112 (73.2)	122 (79.7)	0.178
Glucocorticoid therapy		53 (34.6)	54 (35.3)	0.905
Ig therapy		35 (22.9)	32 (20.9)	0.678
Supplemental oxygen		92 (60.1)	91 (59.5)	0.907
Noninvasive mechanical ventilation		8 (5.2)	21 (13.7)	**0.011**
Invasive mechanical ventilation		4 (2.6)	11 (7.2)	0.064
CRRT		1 (0.7)	3 (1.9)	0.623
ECMO		0	1 (0.7)	1.000
Prognosis				**0.017**
Death		16 (10.5)	31 (20.3)	—
Survival		137 (89.5)	122 (79.7)	—

Data are expressed as median (IQR), n (%), or n/N (%), where N is available total cases. Boldface P values are statistically significant ($P < 0.05$). ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate.

The primary outcome was the in-hospital mortality of COVID-19 patients with diabetes and risk factors for the death of patients with diabetes. The secondary outcomes were the clinical characteristics, laboratory findings, incidence of complications, and the differences of risk factors for in-hospital death in COVID-19 patients with and without diabetes.

Statistical Analysis

We made no assumptions regarding missing data. Categorical variables are described as frequencies and percentages based on the available data. Continuous variables are described as the medians and IQRs. We used the Pearson χ^2 test, the Mann-Whitney test, and the Fisher exact test for comparisons between patients with and without diabetes and between survivors and nonsurvivors, as appropriate.

To explore the risk factors associated with in-hospital death for the 306 COVID-19 patients and to assess whether diabetes was an independent risk factor for death, a multivariable Cox proportional hazards regression model was performed. Four variables, including diabetes, hypertension, cardiovascular disease, and chronic pulmonary disease, were included in the model. Age and sex were not included because the patients with and without diabetes were matched on age and sex. We also conducted Cox regression analyses to identify risk factors for in-hospital death of patients with diabetes and matched patients without diabetes. Considering the death toll was not large in our study, and to avoid overfitting in the model, five variables, including age, sex, underlying hypertension, cardiovascular disease, and chronic pulmonary disease, were chosen for the final regression models. All the variables included in the final models were based on clinical and scientific understanding, previous findings, and the results of univariable analyses. Variables were excluded from the Cox regression models if the number of events was too small (i.e., chronic kidney disease, cerebrovascular disease).

Survival curves for patients with diabetes and matched patients without diabetes were developed using the Kaplan-Meier method with the log-rank test. The statistical analyses were conducted with SPSS (version 25.0), GraphPad Prism (version 5.0), and R (version 3.6.1) software. A two-sided P value <0.05 was considered statistically significant.

RESULTS

Of 1,561 COVID-19 patients, 153 patients (42 from Zhongnan Hospital and 111 from Renmin Hospital) with diabetes were included, and the prevalence of diabetes was 9.8%. The median age of the patients with diabetes was 64.0 (IQR, 56.0–72.0) years. The patients with and without diabetes were well matched for age and sex, with men and women represented approximately equally (Table 1). More patients with diabetes reported no exposure history but had a higher prevalence of hypertension (56.9% vs. 28.8%), cardiovascular disease (20.9% vs. 11.1%), and cerebrovascular disease (7.8% vs. 1.3%) (all P values <0.05). Fever and cough were the most common onset of symptoms in both groups. Patients with diabetes were more likely to require intensive care unit (ICU) admission (17.6% vs. 7.8%, $P < 0.05$). The characteristic ground-glass opacity on CT images is shown in Supplementary Fig. 1. Among laboratory findings, patients with diabetes had lower levels of cholesterol (3.8 vs. 4.1 mmol/L), Pa_{O_2} (68.5 vs. 88.0 mmHg) and $CD8^+$ cell count (164.0 vs. 242.0/μL), and higher levels of blood glucose (9.4 vs. 5.7 mmol/L) and procalcitonin (0.06 vs. 0.05 ng/mL) (all P values <0.05). Patients with diabetes were more likely to have ARDS (24.8% vs. 11.1%), acute cardiac injury (30.7% vs. 17.0%), secondary

Table 2—Characteristics, laboratory findings, complications, treatments, and outcomes of survivors and nonsurvivors among COVID-19 patients with diabetes and matched patients without diabetes

		Patients without diabetes		Patients with diabetes	
		Survivors (n = 137)	Nonsurvivors (n = 16)	Survivors (n = 122)	Nonsurvivors (n = 31)
Age, years		63.0 (56.0–70.0)	72.0 (68.0–81.0)*	63.0 (56.0–69.0)	76.0 (65.0–82.0)†
Sex					
Female		68 (49.6)	10 (62.5)	69 (56.6)	9 (29.0)†
Male		69 (50.4)	6 (37.5)	53 (43.4)	22 (71.0)†
Exposure history		28 (20.4)	3 (18.8)	14 (11.5)	4 (12.9)
Smoking		9 (6.6)	0	4 (3.3)	3 (9.7)
Drinking		7 (5.1)	0	5 (4.1)	1 (3.2)
Comorbidities					
Hypertension		38 (27.7)	6 (37.5)	61 (50.0)	26 (83.9)†
Cardiovascular disease		14 (10.2)	3 (18.8)	18 (14.8)	14 (45.2)†
Cerebrovascular disease		0	2 (12.5)*	7 (5.7)	5 (16.1)
Chronic pulmonary disease		10 (7.3)	3 (18.8)	4 (3.3)	4 (12.9)
Chronic kidney disease		3 (2.2)	3 (18.8)*	4 (3.3)	2 (6.5)
Chronic liver disease		4 (2.9)	0	5 (4.1)	0
Malignancy		4 (2.9)	2 (12.5)	6 (4.9)	2 (6.5)
Signs and symptoms					
Fever		106 (77.4)	12 (75.0)	95 (77.9)	25 (80.6)
Cough		69 (50.4)	9 (56.3)	77 (63.1)	18 (58.1)
Dyspnea		49 (35.8)	11 (68.8)*	35 (28.7)	17 (54.8)†
Myalgia		15 (10.9)	1 (6.3)	18 (14.8)	4 (12.9)
Headache		6 (4.4)	0	3 (2.5)	0
Diarrhea		20 (14.6)	3 (18.8)	17 (13.9)	1 (3.2)
Nausea or vomiting		5 (3.6)	0	6 (4.9)	2 (6.5)
Anorexia		71 (51.8)	11 (68.8)	63 (51.6)	18 (58.1)
Fatigue		70 (51.1)	9 (56.3)	73 (59.8)	22 (71.0)
From onset symptom to, days					
Hospital admission		10.0 (7.0–15.0)	10.0 (7.0–14.0)	11.0 (7.0–20.0)	10.0 (5.0–15.0)
Confirmation of SARS-CoV-2		8.0 (4.0–12.0)	9.0 (6.0–12.0)	8.0 (4.0–14.0)	9.0 (3.0–14.0)
Hospital length of stay, days		16.0 (10.0–22.0)	4.0 (3.0–8.0)*	17.0 (11.0–23.0)	6.0 (2.0–11.0)†
ICU admission		2 (1.5)	10 (62.5)*	7 (5.7)	20 (64.5)†
Respiratory rate, rpm		20.0 (18.0–20.0)	21.0 (17.0–34.0)	20.0 (18.0–20.0)	21.0 (18.0–29.0)†
Heart rate, bpm		85.0 (76.0–92.0)	79.0 (70.0–97.0)	82.0 (78.0–91.0)	88.0 (82.0–108.0)†
Mean arterial pressure, mmHg		95.0 (87.0–102.0)	98.0 (87.0–115.0)	94.0 (87.0–100.0)	95.0 (86.0–103.0)
CT manifestations, area of lung injury					
<25%		81/115 (70.4)	0*	68/105 (64.8)	6/16 (37.5)†
25–50%		19/115 (16.5)	0	16/105 (15.2)	5/16 (31.3)
50–75%		10/115 (8.7)	0	18/105 (17.3)	1/16 (6.3)
>75%		3/115 (2.6)	3/3 (100.0)*	4/105 (3.8)	4/16 (25.0)†
Laboratory findings	Normal range				
Average RBG, mmol/L	<11.1	NA	NA	7.6 (6.2–10.4)	13.6 (10.4–17.3)†
HbA_{1c}, %	3.6–6.0	NA	NA	7.9 (6.6–9.1)	9.9 (8.4–11.4)
HbA_{1c}, mmol/mol	16.0–42.0	NA	NA	63.0 (49.0–76.0)	85.0 (68.0–101.0)
White blood cell count, $\times 10^9$/L	3.5–9.5	5.2 (4.0–7.1)	9.6 (6.9–13.4)*	5.4 (4.4–7.1)	8.0 (5.4–13.8)†
Neutrophil count, $\times 10^9$/L	1.8–6.3	3.3 (2.5–4.9)	8.0 (5.1–11.7)*	3.5 (2.6–4.9)	6.6 (4.2–12.4)†
Lymphocyte count, $\times 10^9$/L	1.1–3.2	1.1 (0.9–1.6)	0.5 (0.4–1.2)*	1.2 (0.8–1.7)	0.7 (0.4–0.8)†
Platelet count, $\times 10^9$/L	125–350	222.0 (165.0–289.0)	205.0 (136.0–226.0)	202.0 (147.0–279.5)	178.0 (126.8–203.8)†
C-reactive protein, mg/L	0–10	10.8 (5.0–47.4)	115.2 (34.3–192.2)*	11.6 (5.0–62.5)	85.5 (45.4–170.0)†
Prothrombin time, s	9–13	12.0 (11.3–12.5)	12.7 (12.0–14.4)*	11.9 (11.4–12.7)	12.9 (11.6–13.8)†
D-dimer, mg/L	0–550	520.0 (250.0–1,102.3)	4,330.0 (1,510.0–17,140.0)*	495.0 (240.5–1,306.3)	2,545.0 (782.0–7,830.0)†
ALT, units/L	9–50	22.0 (15.8–38.0)	29.0 (20.3–71.5)	25.0 (16.0–35.5)	23.0 (17.8–43.5)
Creatinine, μmol/L	57–111	61.0 (51.0–76.3)	73.5 (59.9–97.8)*	61.8 (49.0–73.3)	85.5 (68.0–159.4)†
eGFR, mL/min	>90	97.4 (85.2–107.7)	73.0 (56.3–90.1)*	97.3 (84.7–106.4)	70.0 (38.1–86.6)†
Total cholesterol, mmol/L	<5.2	4.1 (3.4–5.0)	3.9 (3.1–4.2)	3.8 (3.3–4.3)	3.8 (2.9–4.1)
Triglyceride, mmol/L	<1.70	1.3 (1.0–1.7)	1.4 (1.0–1.6)	1.3 (1.0–1.7)	1.6 (1.2–2.6)†
pH	7.35–7.45	7.41 (7.39–7.43)	7.37 (7.28–7.48)	7.40 (7.37–7.46)	7.42 (7.35–7.45)
Pa_{O_2}, mmHg	80–100	91.5 (74.3–115.5)	55.5 (39.5–74.8)*	89.0 (60.0–122.0)	55.0 (44.0–60.0)†

Continued on p. 1387

Table 2—Continued

		Patients without diabetes		Patients with diabetes	
		Survivors (n = 137)	Nonsurvivors (n = 16)	Survivors (n = 122)	Nonsurvivors (n = 31)
Spo_2, %	95–100	97.0 (95.0–99.0)	87.0 (78.3–89.8)*	97.0 (94.0–98.0)	89.0 (79.0–93.0)†
Glucose, mmol/L	<11.1	5.7 (4.8–7.0)	7.1 (5.1–12.2)	8.5 (6.6–12.1)	12.7 (8.8–18.6)†
Lactate, mmol/L	0.5–1.5	2.1 (1.3–2.7)	2.4 (2.1–6.0)*	1.8 (1.5–2.5)	2.3 (1.9–3.3)†
Procalcitonin, ng/mL	<0.1	0.05 (0.04–0.07)	0.14 (0.10–0.48)*	0.05 (0.04–0.10)	0.47 (0.15–1.40)†
Ultrasensitive troponin I, ng/mL	0–0.04	0.006 (0.006–0.010)	0.06 (0.014–0.506)*	0.006 (0.006–0.012)	0.070 (0.018–0.189)†
$CD3^+$ cell count, /μL	723–2,737	706.0 (491.5–1,004.5)	266.5 (173.8–579.8)*	657.5 (431.0–1,035.3)	297.0 (139.0–433.0)†
$CD4^+$ cell count, /μL	404–1,612	396.0 (293.0–599.0)	130.5 (92.0–369.8)*	442.5 (264.5–676.0)	130.0 (103.0–277.0)†
$CD8^+$ cell count, /μL	220–1,129	268.0 (157.0–396.0)	106.5 (42.0–212.5)*	221.0 (128.3–312.0)	68.0 (52.0–156.0)†
$CD19^+$ cell count, /μL	80–616	139.0 (91.5–221.5)	88.5 (54.8–175.0)	149.5 (111.3–237.0)	75.0 (45.0–163.0)†
$CD16^+56^+$ cell count, /μL	84–724	132.5 (71.8–196.3)	51.0 (24.3–124.0)*	137.5 (81.3–224.8)	100.0 (40.0–157.0)†
Complications					
ARDS		1 (0.7)	16 (100.0)*	7 (5.7)	31 (100.0)†
AKI		1 (0.7)	4 (25.0)*	3 (2.5)	16 (51.6)†
Acute cardiac injury		15 (10.9)	11 (68.8)*	17 (13.9)	30 (96.8)†
Shock		0	16 (100.0)*	2 (1.6)	30 (96.8)†
Secondary infection		19 (13.9)	9 (56.3)*	17 (13.9)	20 (64.5)†
Treatments					
Antiviral therapy		130 (94.9)	16 (100.0)	117 (95.9)	31 (100.0)
Antibiotic therapy		96 (70.1)	16 (100.0)*	91 (74.6)	31 (100.0)†
Glucocorticoid therapy		40 (29.2)	13 (81.3)*	37 (30.3)	17 (54.8)†
Ig therapy		28 (20.4)	7 (43.8)	22 (18.0)	10 (32.3)
Supplemental oxygen		76 (55.5)	16 (100.0)*	65 (53.3)	26 (83.9)†
Noninvasive mechanical ventilation		1 (0.7)	7 (43.8)*	5 (4.1)	16 (51.6)†
Invasive mechanical ventilation		0	4 (25.0)*	2 (1.6)	9 (29.0)†
CRRT		0	1 (6.3)	1 (0.8)	2 (6.5)
ECMO		0	0	1 (0.8)	0

Data are expressed as median (IQR), n (%), or n/N (%), where N is available total cases. ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NA, not available. *$P < 0.05$ (statistically significant) between nonsurvivors and survivors among patients without diabetes. †$P < 0.05$ (statistically significant) between nonsurvivors and survivors among patients with diabetes.

infections (24.2% vs. 11.1%), shock (20.9% vs. 10.5%), and AKI (12.4% vs. 3.3%) (all P values <0.05). Antiviral therapy, antibacterial therapy, and supplemental oxygen were the most common treatments in both groups. Among all of the treatment strategies, only noninvasive mechanical ventilation (13.7% vs. 5.2%, $P < 0.05$) was applied more commonly in patients with diabetes. Death was more common in patients with diabetes (20.3% vs. 10.5%, $P < 0.05$).

Diabetes history regarding duration, previous glycemic condition, previous glucose control methods, and complications are reported in Supplementary Table 1. Among patients with diabetes who died compared with survivors (Table 2), they were older (76.0 vs. 63.0 years), most were male (71.0% vs. 29.0%), and were more likely to have hypertension (83.9% vs. 50.0%), cardiovascular disease (45.2% vs. 14.8%), and present with dyspnea (54.8% vs. 28.7%) (all P values <0.05). CT analysis of the lungs in nonsurvivors revealed a higher proportion of patients with >75% involvement and fewer with <25% involvement compared with survivors. Compared with survivors, nonsurvivors had higher respiratory rate (21 vs. 20 rpm) and heart rate (88 vs. 82 bpm) (all P values <0.05). Nonsurvivors were more likely to be admitted to the ICU (64.5% vs. 5.7%) but had a significantly shorter hospital length of stay (6.0 vs. 17.0 days) (all P values <0.05). Average RBG (13.6 vs. 7.6 mmol/L, $P < 0.05$) and numerous laboratory parameters, including lymphocyte count, D-dimer concentration, triglyceride level, and oxygen saturation (Spo_2) among others, distinguished nonsurvivors from survivors (Table 2). The daily average RBG during the first consecutive 5 days of hospitalization tracked in 13 nonsurvivors and 32 survivors showed that nonsurvivors had a significantly higher average RBG (except day 2) (Supplementary Fig. 2*A*). Compared with survivors, nonsurvivors were more likely to have ARDS (100.0% vs. 5.7%), acute cardiac injury (96.8% vs. 13.9%), shock (96.8% vs. 1.6%), secondary infections (64.5% vs. 13.9%), and AKI (51.6% vs. 2.5%) (all P values <0.05). With regard to treatments, nonsurvivors were more often treated with antibiotics (100.0% vs. 74.6%), glucocorticoids (54.8% vs. 30.3%), supplemental oxygen (83.9% vs. 53.3%), noninvasive mechanical ventilation (51.6% vs. 4.1%), and invasive mechanical ventilation (29.0% vs. 1.6%) (all P values <0.05).

Among patients with diabetes, 30 patients with the highest average RBG and 30 patients with the lowest average RBG during hospitalization were analyzed (Supplementary Fig. 2*B* and *C*). The median average RBG levels were 16.4 (IQR, 14.9–17.6) mmol/L and 5.9 (IQR, 5.3–6.1) mmol/L, respectively. Half of the patients with the highest RBG had sustained detectable SARS-CoV-2 virus until death, while the RT-PCR tests turned negative in most patients with the lowest average RBG. In addition, we found that 16 of 30 patients with the highest average RBG died, whereas only 1 of 30 patients with the lowest average RBG died.

Among matched patients without diabetes who died compared with survivors

Table 3—Cox regression analyses of risk factors for in-hospital death of COVID-19 patients with diabetes and matched patients without diabetes

	Patients without diabetes (N = 153)		Patients with diabetes (N = 153)	
Variables	Univariable HR (95% CI)	Multivariable HR (95% CI)	Univariable HR (95% CI)	Multivariable HR (95% CI)
Demographics and clinical characteristics				
Age ≥70 years	5.28 (1.83–15.21)*	5.87 (1.88–18.33)*	4.87 (2.29–10.34)*	2.39 (1.03–5.56)*
Male sex	0.65 (0.24–1.79)	0.46 (0.16–1.32)	2.56 (1.18–5.56)*	2.10 (0.95–4.65)
Hypertension	1.58 (0.57–4.37)	1.06 (0.35–3.20)	4.48 (1.72–11.69)*	3.10 (1.14–8.44)*
Cardiovascular disease	1.83 (0.52–6.42)	1.08 (0.25–4.70)	3.79 (1.86–7.70)*	1.87 (0.88–4.00)
Chronic pulmonary disease	2.40 (0.68–8.51)	1.21 (0.28–5.15)	3.76 (1.30–10.89)*	2.77 (0.90–8.54)
Laboratory findings				
Average RBG, mmol/L	NA	–	1.23 (1.15–1.32)*	—
White blood cell count, $\times 10^9$/L	1.05 (1.01–1.09)*	–	1.17 (1.09–1.26)*	—
Neutrophil count, $\times 10^9$/L	1.31 (1.19–1.44)*	–	1.24 (1.15–1.34)*	—
Lymphocyte count, $\times 10^9$/L	0.61 (0.25–1.52)	–	0.12 (0.04–0.31)*	—
Platelet count, $\times 10^9$/L	0.993 (0.99–0.999)*	–	1.00 (0.99–1.00)	—
C-reactive protein, mg/L	1.01 (1.008–1.02)*	–	1.01 (1.00–1.02)*	—
Prothrombin time, s	1.78 (1.36–2.33)*	–	1.12 (1.03–1.22)*	—
Creatinine, μmol/L	1.02 (1.01–1.03)*	–	1.01 (1.00–1.01)*	—
eGFR, mL/min	0.96 (0.94–0.98)*	–	0.97 (0.96–0.98)*	—
Total cholesterol, mmol/L	0.57 (0.32–0.10)*	–	0.94 (0.59–1.48)	—
Triglyceride, mmol/L	0.85 (0.42–1.70)	–	1.73 (1.22–2.45)*	—
Pa_{O_2}, mmHg	0.97 (0.95–0.99)*	–	0.96 (0.94–0.99)*	—
Sp_{O_2}, %	0.95 (0.93–0.98)*	–	0.94 (0.92–0.97)*	—
Glucose, mmol/L	1.13 (1.02–1.25)*	–	1.12 (1.05–1.19)*	—
Lactate, mmol/L	1.32 (1.09–1.61)*	–	1.39 (1.13–1.70)*	—
Procalcitonin, ng/mL	2.13 (1.43–3.17)*	–	1.18 (1.04–1.35)*	—
$CD3^+$ cell count, /μL	0.995 (0.992–0.998)*	–	0.997 (0.995–0.999)*	—
$CD4^+$ cell count, /μL	0.994 (0.990–0.998)*	–	0.994 (0.991–0.998)*	—
$CD8^+$ cell count, /μL	0.992 (0.986–0.998)*	–	0.994 (0.989–0.999)*	—
$CD19^+$ cell count, /μL	1.000 (1.000–1.001)	–	0.991 (0.984–0.998)*	—
$CD16^+56^+$count, /μL	0.987 (0.977–0.998)*	–	0.998 (0.994–1.002)	—

eGFR, estimated glomerular filtration rate; NA, not available. *$P < 0.05$ (statistically significant).

(Table 2), they were older (72.0 vs. 63.0 years), more likely to have cerebrovascular disease (12.5% vs. 0), chronic kidney disease (18.8% vs. 2.2%), and present with dyspnea (68.8% vs. 35.8%) (all P values <0.05). Nonsurvivors were more likely to be admitted to the ICU (62.5% vs. 1.5%, $P < 0.05$). Laboratory findings, treatments, and complications are reported in Table 2.

Among the included 306 patients, multivariable analyses (Supplementary Table 2) showed that hypertension (HR 2.50, 95% CI 1.30–4.78), cardiovascular disease (HR 2.24, 95% CI 1.19–4.23), and chronic pulmonary disease (HR 2.51, 95% CI 1.07–5.90) were independent risk factors for in-hospital death. Diabetes (HR 1.58, 95% CI 0.84–2.99) was not independently associated with death after adjusting for covariables. In univariable analyses for patients with diabetes (Table 3), 23 variables, including age, male sex, hypertension, chronic pulmonary disease, cardiovascular disease, higher average RBG, and decreased lymphocyte count, among others, were related to death. In multivariable analyses, age ≥70 years (HR 2.39, 95% CI 1.03–5.56) and hypertension (HR 3.10, 95% CI 1.14–8.44) were independent risk factors for in-hospital death of patients with diabetes. For matched patients without diabetes (Table 3), Cox regression analyses indicated that age ≥70 years (HR 5.87, 95% CI 1.88–18.33) was independently associated with death. The survival curves of COVID-19 patients with diabetes and matched patients without diabetes are shown in Fig. 1.

CONCLUSIONS

This study analyzed the characteristics of COVID-19 patients with diabetes and sex- and age-matched patients without diabetes and identified the risk factors associated with in-hospital death of these patients. Among patients hospitalized with COVID-19, the prevalence of diabetes was 9.8%. Patients with diabetes had more underlying comorbidities, were more likely to suffer complications, had a higher proportion of ICU admissions, and more deaths compared with sex- and age-matched patients without diabetes. However, underlying hypertension, cardiovascular disease, and chronic pulmonary disease, rather than diabetes, were independently associated with in-hospital death of COVID-19 patients. Among patients with diabetes, age ≥70 years and underlying hypertension were independent risk factors for in-hospital death.

The most common symptoms of SARS-CoV-2 infection in patients with diabetes included fever, cough, and dyspnea, which were consistent with recent publications (20,21). A previous study showed that diabetes tripled the risk of hospitalization after pandemic influenza A H1N1 and significantly increased the risks of ICU admission and mortality (14,22). In our study, patients with diabetes had a significantly higher mortality and more severe disease, as verified by the higher proportion of ICU cases and the higher incidences of ARDS and multiple organ dysfunction syndrome as well as

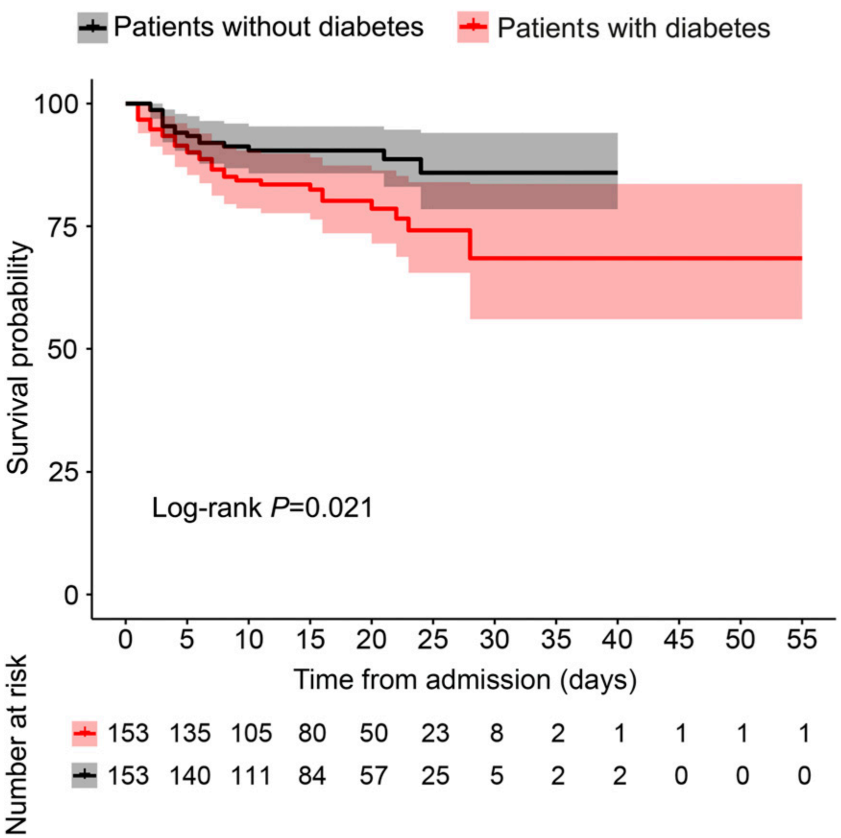

Figure 1—Survival curves of COVID-19 patients with diabetes and matched patients without diabetes. The gray and pink areas represent 95% CIs.

secondary infections even after sex and age adjustment.

The worse outcomes of COVID-19 patients with diabetes could be associated with underlying comorbidities. A nationwide analysis in China showed that the most prevalent comorbidity in COVID-19 patients was hypertension (16.9%), followed by diabetes (8.2%), and that the underlying diseases were associated with adverse outcomes of COVID-19 patients (23). In our study, hypertension and cardiovascular disease were more common in patients with diabetes. Although diabetes itself was not independently associated with death of COVID-19 patients in our multivariable analyses, diabetes and other comorbidities, which included cardiovascular disease and hypertension, were often closely related, and the effect of these factors could not be considered separately. Diabetes and hypertension often coexist and may act synergistically to promote adverse clinical events (24,25). The persistent hyperglycemic condition and metabolism changes in diabetes together with coexisting hypertension lead to microvascular and macrovascular changes and form a vicious cycle that further contributes to cardiovascular events (26). Recent study also suggested that hypertension was associated with increased risk of severe and fatal COVID-19, and ACE inhibitors reduced the mortality in COVID-19 patients with hypertension (27,28). This evidence further supported our finding that hypertension was independently associated with death among patients with diabetes. Thus, patients with diabetes with underlying comorbidities, especially hypertension, should attract more attention. In sex- and age-matched patients without diabetes, Cox regression analyses did not reveal underlying comorbidities as risk factors associated with death. This might be explained by the absence of diabetes and the relatively lower prevalence of other comorbidities in the matched population.

A recent publication demonstrated that old age was an independent predictor of mortality in COVID-19 patients (3). The age-dependent decreases in cellular and humoral immune function in elderly patients have been reported before, especially with regard to adaptive immune function (29). In our study, nonsurvivors among patients with diabetes were older compared with survivors and had obvious lymphopenia as demonstrated by significantly lower numbers of T and B cells. Furthermore, the high risks of elderly patients with diabetes could be due to their poor overall health condition and greater number of comorbidities.

Besides the above-mentioned independent risk factors, other potential risk factors related to death were also identified by our univariable analyses. Recent studies revealed lymphopenia as an important characteristic of SARS-CoV-2 infection, especially in critically ill and deceased patients (2,12). Besides, infection and destruction of lymphocytes by the SARS-CoV have been proven (30). Thus, the destruction of lymphocytes by the SARS-CoV-2 virus might be speculated but needs to be further investigated. Lymphopenia was also noticed in our study, especially in patients with diabetes. This might be explained by the previous findings that diabetes and hyperglycemia could impair the innate and adaptive immunity (31,32).

During hospitalization, underlying diabetes, illness severity, and medical treatments could contribute to the hyperglycemic condition. Hyperglycemia has been proven to be associated with increased risks of in-hospital complications and in-hospital death (33,34). In our study, we also noticed higher blood glucose levels during hospitalization in patients with diabetes who did not survive than in survivors. Thus, frequent monitoring of blood glucose and the use of oral glucose-lowering medication or insulin would be important routine procedures for patients with diabetes.

Besides the findings in our study, some other factors might also contribute to the mortality of COVID-19 patients, among which obesity would be a potential candidate. A recent study in the New York area showed that 41.7% of the patients were obese, and an increasing number of reports have linked obesity to more severe COVID-19 illness (35–37).

Despite the importance of the aforementioned findings, the current study, however, has some limitations. Firstly, data collection relied on electronic medical records. CT images of some patients transferred from other hospitals were not available in the electronic medical record systems of these two hospitals. Some important indicators were not tested in all patients. Thus, the missing data might lead to bias. Secondly, these two hospitals are designated for treatment of patients with relatively severe infection, which to some extent might lead to a higher mortality. Thirdly, the sample size and relatively small number of deaths might influence the interpretation of our findings. Fourthly, the possibility of obesity as a contributor to death in COVID-19 patients was not investigated due to the lack of information on BMI. Fifthly, patients in this study were selected on the basis of diabetes status and death or discharge. Some patients who remained alive in these two hospitals at the time of the analysis were not included in this study. Finally, because a matched design was used in our study, the roles of sex and age in the death of patients with diabetes versus those without could not be examined and should be addressed further.

In summary, the findings of our study suggested that COVID-19 patients with diabetes had worse outcomes compared with the sex- and age-matched patients without diabetes. Diabetes was not independently associated with in-hospital death, while hypertension, cardiovascular disease, and chronic pulmonary disease played more important roles in contributing to the mortality of COVID-19 patients. In-hospital death among COVID-19 patients with diabetes was associated with hypertension and advanced age, whereas only older age was independently associated with death among matched patients without diabetes. The need for early monitoring and supportive care should be addressed in these patients at high risks.

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