Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication

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Diabetes Care 2020;43:1399–1407 | https://doi.org/10.2337/dc20-0660

OBJECTIVE

Diabetes is one of the most distinct comorbidities of COVID-19. Here, we describe the clinical characteristics of and outcomes in patients with diabetes in whom COVID-19 was confirmed or clinically diagnosed (with typical features on lung imaging and symptoms) and their association with glucose-lowering or blood pressure–lowering medications.

RESEARCH DESIGN AND METHODS

In this retrospective study involving 904 patients with COVID-19 (136 with diabetes, mostly type 2 diabetes), clinical and laboratory characteristics were collected and compared between the group with diabetes and the group without diabetes, and between groups taking different medications. Logistic regression was used to explore risk factors associated with mortality or poor prognosis.

RESULTS

The proportion of comorbid diabetes is similar between cases of confirmed and of clinically diagnosed COVID-19. Risk factors for higher mortality of patients with diabetes and COVID-19 were older age (adjusted odds ratio [aOR] 1.09 [95% CI 1.04, 1.15] per year increase; $P = 0.001$) and elevated C-reactive protein (aOR 1.12 [95% CI 1.00, 1.24]; $P = 0.043$). Insulin usage (aOR 3.58 [95% CI 1.37, 9.35]; $P = 0.009$) was associated with poor prognosis. Clinical outcomes of those who use an ACE inhibitor (ACEI) or angiotensin II type-I receptor blocker (ARB) were comparable with those of patients who do not use ACEI/ARB among COVID-19 patients with diabetes and hypertension.

CONCLUSIONS

C-reactive protein may help to identify patients with diabetes who are at greater risk of dying during hospitalization. Older patients with diabetes were prone to death related to COVID-19. Attention needs to be paid to patients with diabetes and COVID-19 who use insulin. ACEI/ARB use showed no significant impact on patients with diabetes and hypertension who have COVID-19.

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Received 28 March 2020 and accepted 24 April 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.12194748.

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This article is part of a special article collection available at https://care.diabetesjournals.org/collection/diabetes-and-COVID19.

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV) (1–3). The outbreak of COVID-19 rapidly caused a global health crisis (4–7), and the World Health Organization has announced COVID-19 as a pandemic.

Diabetes is one of the most frequent comorbidities reported in patients with COVID-19. Among patients with confirmed COVID-19, the proportion with comorbid diabetes was 22% in one study of 191 patients (2), and 16.2% in another cohort of 1,099 patients (3). Notably, a report of 72,314 COVID-19 cases found higher mortality in patients with diabetes (7.3% vs. 2.3% overall) (6). Further investigations into COVID-19 cases are necessary in order to elaborate the differences between those with comorbid diabetes and those without, and consequently to help identify risk factors for COVID-19. Moreover, little is known about the impact of sex and glucose-lowering medication on the characteristics and prognosis of patients with diabetes and COVID-19. Relevant analyses, including of important laboratory parameters and glucose-lowering medications, can provide information on risk factors, which may shed light on a tailored therapeutic strategy for patients with diabetes and COVID-19.

Notably, the diagnostic criteria of COVID-19 have undergone a series of adjustments according to updated understanding about the disease. Generally, COVID-19 is confirmed by positive SARS-CoV-2 nucleic acid test results (6). However, because of the difficulty in obtaining reliable nasopharyngeal swab specimens, the timing of detection, and the limited detection capacity early in the outbreak, false-negative results are often seen (8,9). For some SARS-CoV-2-infected patients who rarely show prominent upper respiratory tract signs and symptoms (1), the virus concentration of SARS-CoV-2 may be too low for accurate detection with a nasopharyngeal swab. Therefore, in addition to nucleic acid testing, lung computed tomography (CT) features have also been included as a clinical diagnostic criteria for patients within Hubei Province per the Diagnosis and Treatment Plan for COVID-19 issued by the National Health Commission (NHC) of China (fifth edition, 5 February 2020) (10); this was revised in the sixth edition (19 February 2020) (11). Accordingly, patients (in Hubei Province) were clinically diagnosed with COVID-19 on the basis of symptoms, exposure, and presence of lung imaging features consistent with coronavirus pneumonia, and those who were further tested as being positive for SARS-CoV-2 were classified as having confirmed COVID-19. Patients with COVID-19 in both categories are required to undergo strict quarantine and clinical observation and treatment in Fangcang shelter hospitals or designated hospitals (12).

Here, we evaluate the clinical characteristics of patients with COVID-19 with or without comorbid diabetes, and provide specific information about those cases regarding routine usage of glucose-lowering or blood pressure–lowering medicines, the medications most commonly used by patients with diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This retrospective study included 904 patients aged 15–99 years who were admitted to the Central Hospital of Wuhan from 1 January 2020 and enrolled with a definite outcome (discharged from or died in the hospital); the data cutoff for the study was 17 March 2020. The patients included in this study have not, to our knowledge, been reported previously. The Central Hospital of Wuhan, located in an urban area of Wuhan, is a class A tertiary comprehensive hospital and one of the hospitals designated to treat patients with COVID-19 who are in moderate, severe, or critical condition. Patients with mild disease, who accounted for the majority of total COVID-19 cases and were cared for in Fangcang shelter hospitals (12,13), were not included in our study; thus this cohort study represents the severe end of COVID-19. Most patients included in this study were local residents.

All patients were diagnosed with COVID-19 according to the Diagnosis and Treatment Plan for COVID-19 issued by the NHC of China (fifth edition) (10). Diabetes was ascertained through a diabetes diagnosis in medical records or a self-reported diagnosis confirmed by medical records reviewed by endocrinologists. Diabetes was defined according to the World Health Organization diagnostic criteria: fasting plasma glucose $\geq$7.0 mmol/L ($\geq$126 mg/dL) or 2-h plasma glucose $\geq$11.1 mmol/L ($\geq$200 mg/dL). Of the 136 patients with diabetes, 120 had type 2 diabetes, 1 had type 1 diabetes, 1 had gestational diabetes and was still pregnant at the time of admission, and 14 did not have diabetes specified in their medical records.

The Research Ethics Commission of the Central Hospital of Wuhan approved this study and waived informed consent from study participants because of the study's retrospective design (approval #2020–40). All clinical investigations were conducted in accordance with the guidelines of the Declaration of Helsinki.

Data Collection

Epidemiological, demographic, clinical, laboratory, treatment-related, and outcome-related data were reviewed and extracted from electronic medical records by experienced clinicians using a standardized data collection form. For the analysis of glucose-lowering medications, we excluded 16 patients with diabetes whose history of glucose-lowering medicine use was unavailable. In the analysis of blood pressure–lowering medication, we included 71 patients with diabetes who also had COVID-19 and comorbid hypertension and who had available a history of blood pressure–lowering drug use.

Procedures

Briefly, clinical diagnosis of COVID-19 was made on the basis of symptoms, exposure, and the presence of lung imaging features consistent with coronavirus pneumonia. SARS-CoV-2 infection was detected in respiratory specimens by using next-generation sequencing or real-time fluorescent RT-PCR, as previously described (1). Patients underwent routine laboratory examinations such as blood examinations, coagulation tests, biochemical tests (including liver and renal function, creatine kinase, lactate dehydrogenase, and electrolytes). Chest imaging was acquired by CT. The clinical outcomes were evaluated by experienced clinicians.

Definitions

Fever was defined as an axillary temperature of at least 37.3°C. The COVID-19 severity grading (mild, moderate, severe, or critical) was defined according to the

Diagnosis and Treatment Plan for COVID-19 issued by the NHC of China. Briefly, mild grade was defined as mild symptoms and no changes on lung CT scans; moderate grade was defined as fever, respiratory symptoms, and changes on lung CT scans; severe grade was defined as respiratory rate ≥30 breaths per min, blood oxygen saturation ≤93%, oxygenation index ≤300 mmHg, and/or lung infiltrates increased >50% within 24–48 h; and critical grade was defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Poor prognosis includes progression to severe or critical illness and in-hospital death.

Statistical Analysis

Categorical variables are the number (percentage), and continuous variables are the median (interquartile range [IQR]). Categorical data were compared by using the χ^2 test or the Fisher exact test, as appropriate. Nonnormal continuous data were compared with the Mann-Whitney *U* test. Sample size varied because items included in patient examinations may have differed, as they were determined by different treating physicians and dependent on patients' symptoms and comorbidities (Supplementary Table 1). Logistic regression was used in order to perform univariable and multivariable analysis for determination of odds ratios (ORs) and 95% CIs for factors associated with clinical outcomes; the results were not adjusted for multiple tests. Laboratory findings tested in no more than half of the total cases were not included in regression models in order to avoid possible bias. Analyses of different factors were based on nonmissing data. We chose age, albumin, creatinine, C-reactive protein (CRP), and glucose as five variables in multivariable regression models to identify risk factors for in-hospital death or poor prognosis in all patients with COVID-19—those with and those without diabetes. In order to explore the association of medication and outcomes for patients with COVID-19 with diabetes who use glucose-lowering medication, age, albumin, creatinine, glucose, CRP, and usage of a specific medication (yes/no) were chosen as six variables in the corresponding multivariable regression model. A P value <0.05 was considered statistically significant. Analyses were performed with SPSS software (version 22.0; IBM) unless otherwise indicated.

RESULTS

Demographics and Characteristics of the Study Population

Of the 904 cases included in this study (Table 1), 421 patients (46.57%) were male and 483 (53.43%) were female. The median age was 56.0 years (IQR 39.0–67.0 years), with only three patients under 20 years old. All the patients were clinically diagnosed with COVID-19, and 341 (37.72%) had confirmed COVID-19. The most common symptoms were fever (576 patients [63.72%]), cough (443 patients [49.00%]), and fatigue (212 patients [23.45%]). Hypertension (273 patients [30.20%]) was the most common comorbidity, followed by diabetes (136 patients [15.04%]), cardiovascular disease (91 patients [10.07%]), and nervous system disease (52 patients [5.75%]). At hospital admission, the COVID-19 severity grading was moderate in 89.93% of the cases, severe in 9.07%, and critical in 1.00%. Among the patients, 92 (10.18%) died during hospitalization, and 381 progressed to severe (291 patients [32.19%]) or critical (90 patients [9.96%]) illness.

No significant difference in initial symptoms was seen between the groups with confirmed and clinically diagnosed COVID-19 (Table 1). Compared with confirmed cases, patients with clinically diagnosed COVID-19 were younger (median age 53.0 years [IQR 37.0–66.0 years] vs. 58.0 years [42.0–62.0 years]; P = 0.020), had a higher proportion of moderate cases at admission (91.65% vs. 87.10% patients; P = 0.030), and had a lower rate of progression to critical illness (7.99% vs. 13.20% patients; P = 0.012) and death (6.75% vs. 15.84% patients; P < 0.001) (Table 1). The frequency of hypertension, cardiovascular disease, nervous system disease, chronic kidney disease, and chronic lung disease was higher among confirmed cases than clinically diagnosed cases, whereas the proportion of diabetes was similar between the two groups (14.37% vs. 15.45% patients; P = 0.702) (Table 1).

Baseline Characteristics and Laboratory Indices

Baseline characteristics and laboratory indices of all the patients are provided in Table 2. For patients without diabetes, the overall laboratory findings in those with confirmed COVID-19 were more malignant than in those with clinically diagnosed COVID-19; these findings were consistent with a significantly longer hospital stay, a larger proportion with a poor prognosis, and higher mortality (Table 2). For patients with diabetes, the overall laboratory findings in those with confirmed COVID-19 were similar to such findings in patients with clinically diagnosed COVID-19, except for a longer hospital stay (median 26.0 days [IQR 19.0–38.0 days] vs. 20.0 days [15.0–28.0 days]; P = 0.004) (Table 2). Among those with confirmed COVID-19, patients with diabetes were older (median age 66.0 years [IQR 60.5–73.5 years]), had a larger proportion with comorbid hypertension (61.22%), and had a longer hospital stay (median 26.0 days [IQR 19.0–38.0 days]). Some of their laboratory indices were more malignant, including significantly higher D-dimer (median 0.72 mg/L [IQR 0.48–2.18 mg/L] vs. 0.50 mg/L [0.23–1.15 mg/L]; P = 0.001) and urea (4.78 mmol/L [3.71–7.95 mmol/L] vs. 4.10 mmol/L [3.20–5.60 mmol/L]; P = 0.003), as well as lower albumin (36.2 g/L [34.05–39.45 g/L] vs. 39.8 g/L [35.6–43.4 g/L]; P < 0.001). Such differences between patients with and those without diabetes were consistently observed in clinically diagnosed cases (Table 2) and were independent of sex (Supplementary Table 2). Some differences between patients with and those without diabetes were significant only for those who had clinically diagnosed COVID-19; these differences included elevated levels of creatinine, creatine kinase, and lactate dehydrogenase (LDH); higher infection-related indices; and higher rates of in-hospital death and poor prognosis (Table 2).

Sex-Dependent Characteristics

Data that were respectively analyzed in male and female patients are summarized in Supplementary Table 2. In confirmed COVID-19 cases, the neutrophil count (median 4.39 × 10^9/L [IQR 3.03–6.74 × 10^9/L]) and LDH (195.00 units/L [178.00–255.00 units/L]), as well as the percentage with comorbid nervous system disease (17.86% [five patients]), were significantly higher among women with diabetes than in women without diabetes, which was consistent with data

Table 1—Demographic characteristics of patients with diagnosed COVID-19

	All patients (n = 904)	Patients with confirmed COVID-19 (n = 341)	Patients with clinically diagnosed COVID-19 (n = 563)
Age, years	56.0 (39.0–67.0)	58.0 (42.0–62.0)	53.0 (37.0–66.0)†
0–19	3 (0.33)	1 (0.29)	2 (0.36)
20–39	237 (26.22)	80 (23.46)	157 (27.89)
40–69	489 (54.09)	182 (53.37)	307 (54.53)
70–99	175 (19.36)	78 (22.87)	97 (17.23)†
Sex			
Male	421 (46.57)	183 (53.67)	238 (42.27)†
Female	483 (53.43)	158 (46.33)	325 (57.73)†
Common initial symptoms			
Fever (temperature ≥37.3°C)	576 (63.72)	216 (63.34)	360 (63.94)
Cough	443 (49.00)	170 (49.85)	273 (48.49)
Fatigue	212 (23.45)	77 (22.58)	135 (23.98)
Dyspnea	122 (13.50)	48 (14.08)	74 (13.14)
Myalgia	117 (12.95)	43 (12.61)	74 (13.14)
Sputum	94 (10.40)	32 (9.38)	62 (11.01)
Diarrhea	47 (5.20)	17 (4.99)	30 (5.33)
Nausea or vomiting	20 (2.21)	5 (1.47)	15 (2.66)
Comorbidities			
Diabetes	136 (15.04)	49 (14.37)	87 (15.45)
Hypertension	273 (30.20)	125 (36.66)	148 (26.29)†
Cardiovascular disease	91 (10.07)	50 (14.66)	41 (7.28)†
Nervous system disease	52 (5.75)	27 (7.92)	25 (4.44)†
Chronic kidney disease	42 (4.65)	24 (7.04)	18 (3.20)†
Chronic lung disease	22 (2.43)	15 (4.40)	7 (1.24)†
Tumor	19 (2.10)	11 (3.23)	8 (1.42)
Initial disease severity			
Moderate	813 (89.93)	297 (87.10)	516 (91.65)†
Severe	82 (9.07)	39 (11.44)	43 (7.64)
Critical	9 (1.00)	5 (1.47)	4 (0.71)
Clinical outcomes			
No progression	431 (47.68)	135 (39.59)	296 (52.58)†
Severe progression	291 (32.19)	107 (31.38)	184 (32.68)
Critical progression	90 (9.96)	45 (13.20)	45 (7.99)†
Death	92 (10.18)	54 (15.84)	38 (6.75)†

Data were n (%) or median (IQR). Data were collected at admission, except for clinical outcomes. †There was a significant difference ($P < 0.05$) between confirmed COVID-19 cases and clinically diagnosed COVID-19 cases. A diagnosis of COVID-19 was based on symptoms, exposure, lung imaging features, and nucleic acid detection of SARS-CoV-2.

from women with clinically diagnosed COVID-19 (Supplementary Table 2). In addition, among men with clinically diagnosed COVID-19, comorbid cardiovascular disease was seen in a larger proportion of men with diabetes (27.91%) than in those without diabetes (8.21%) (P = 0.001) (Supplementary Table 2).

Risk Factors Associated With Mortality or Poor Prognosis

We performed logistic regression for univariable or multivariable analyses to identify risk factors associated with mortality or poor prognosis in this cohort (Table 3 and Supplementary Table 3). Univariable logistic regression analyses showed that increasing odds of in-hospital death or poor prognosis in all patients with COVID-19 were associated with diabetes (in-hospital death: OR 2.51 [95% CI 1.53, 4.13]; poor prognosis: OR 2.21 [95% CI 1.50, 3.26]; both $P < 0.001$) (Table 3).

Considering the inclusion of glucose (highly correlated with diabetes) in multivariable regression models, diabetes was not included as a variable in the analyses. Multivariable regression showed that increasing odds of in-hospital death among patients with diabetes and COVID-19 were associated with older age (adjusted OR [aOR] 1.09 [95% CI 1.04, 1.15] per year increase; P = 0.001) and elevated CRP (aOR 1.12 [95% CI 1.00, 1.24]; P = 0.043) (Table 3). In addition to old age and high CRP, low albumin was an independent risk factor for mortality in patients with COVID-19 who did not have diabetes (Supplementary Table 3). Risk factors for poor prognosis in patients with diabetes and COVID-19 were low albumin (aOR 0.91 [95% CI 0.83, 0.99]; P = 0.030) and high CRP (aOR 1.16 [95% CI 1.01, 1.32]; P = 0.033) (Table 3). Old age and high CRP were independent risk factors for worse prognosis in patients with COVID-19 who did not have diabetes (Supplementary Table 3). Elevated glucose was associated with higher mortality in all patients (aOR 1.08 [95% CI 1.01, 1.16]; P = 0.033) (Table 3) and in patients without diabetes (aOR 1.19 [95% CI 1.01, 1.41]; P = 0.040) (Supplementary Table 3). However, it was not associated with in-hospital death or poor prognosis in patients with diabetes and COVID-19 (Table 3). Age and CRP were independent

Table 2—Clinical characteristics, outcomes, and laboratory findings

	Patients with confirmed COVID-19			Patients with clinically diagnosed COVID-19			*P* value†	
	No Diabetes (n = 292)	Diabetes (n = 49)	*P* value*	No Diabetes (n = 476)	Diabetes (n = 87)	*P* value*	No Diabetes	Diabetes
Baseline characteristics and clinical outcomes								
Age, years	56.0 (38.0–67.0)	66.0 (60.5–73.5)	<0.001	50.0 (35.0–63.0)	66.0 (55.0–72.0)	<0.001	0.003	0.163
Hospital LOS, days	19.0 (12.0–26.0)	26.0 (19.0–38.0)	<0.001	15.0 (10.0–23.0)	20.0 (15.0–28.0)	<0.001	<0.001	0.004
In-hospital death	42 (14.38)	12 (24.49)	0.089	24 (5.04)	14 (16.09)	0.001	<0.001	0.260
Poor prognosis	168 (57.53)	38 (77.55)	0.213	212 (44.54)	55 (63.22)	<0.001	<0.001	0.710
Common initial symptoms								
Fever (temperature ≥37.3°C)	192 (65.75)	24 (48.98)	0.036	305 (64.08)	55 (63.22)	0.812	0.252	0.147
Cough	143 (48.97)	27 (55.10)	0.444	222 (46.64)	51 (58.62)	0.020	0.268	0.721
Fatigue	67 (22.95)	10 (20.41)	0.845	106 (22.27)	29 (33.33)	0.019	0.656	0.119
Comorbidities								
Hypertension	95 (32.53)	30 (61.22)	<0.001	94 (19.75)	54 (62.07)	<0.001	<0.001	1.000
Cardiovascular disease	39 (13.36)	11 (22.45)	0.124	23 (4.83)	18 (20.69)	<0.001	<0.001	0.830
Nervous system disease	19 (6.51)	8 (16.33)	0.039	15 (3.15)	10 (11.49)	0.002	0.028	0.440
Chronic kidney disease	19 (6.51)	5 (10.20)	0.363	7 (1.47)	11 (12.64)	<0.001	<0.001	0.786
Chronic lung disease	13 (4.45)	2 (4.08)	1.000	7 (1.47)	0 (0.00)	0.603	0.018	0.128
Tumor	10 (3.42)	1 (2.04)	0.714	7 (1.47)	1 (1.15)	1.000	0.082	1.000
Laboratory findings								
Hematologic, $\times 10^9$/L								
White blood cells	4.98 (3.83–6.72)	6.02 (4.41–7.43)	0.020	5.31 (4.14–6.64)	5.22 (4.57–7.18)	0.195	0.078	0.463
Neutrophils	3.23 (2.23–4.62)	4.40 (2.87–5.99)	0.001	3.34 (2.36–4.56)	3.78 (2.79–5.34)	0.011	0.509	0.204
Lymphocytes	1.10 (0.75–1.52)	0.91 (0.64–1.31)	0.027	1.29 (0.91–1.73)	1.08 (0.73–1.54)	0.010	<0.001	0.115
Monocytes	0.34 (0.25–0.47)	0.33 (0.25–0.53)	0.888	0.38 (0.27–0.49)	0.39 (0.26–0.52)	0.637	0.078	0.452
Platelets	175.50 (135.25–224.75)	178.00 (136.00–217.50)	0.936	202.50 (165.00–254.75)	188.00 (146.00–235.00)	0.094	<0.001	0.150
Biochemical								
Hemoglobin, g/L	132.00 (119.00–142.75)	123.00 (112.00–134.50)	0.007	128.00 (119.00–139.00)	122.00 (112.00–132.00)	<0.001	0.087	0.667
Albumin, g/L	39.80 (35.60–43.40)	36.20 (34.05–39.45)	<0.001	40.00 (36.40–43.50)	37.00 (33.38–40.30)	<0.001	0.380	0.674
Total bilirubin, μmol/L	9.40 (7.30–13.00)	9.70 (6.70–14.55)	0.750	9.40 (7.00–13.30)	8.90 (5.88–12.55)	0.256	0.766	0.334
ALT, units/L	19.60 (13.80–30.50)	18.60 (12.75–25.50)	0.264	20.70 (13.60–33.68)	21.45 (12.23–34.15)	0.631	0.852	0.427
AST, units/L	22.60 (16.35–34.50)	21.70 (16.15–31.50)	0.334	20.10 (15.70–27.60)	21.45 (15.08–34.15)	0.705	0.002	0.849
LDH, units/L	191.50 (150.00–243.75)	199.00 (175.00–261.00)	0.115	167.00 (139.00–216.75)	198.00 (153.50–271.25)	0.001	<0.001	0.314
Urea, mmol/L	4.10 (3.20–5.60)	4.78 (3.71–7.95)	0.003	3.97 (3.07–4.99)	5.33 (3.80–6.99)	<0.001	0.082	0.881
Creatinine, μmol/L	66.90 (52.98–79.40)	68.60 (48.60–91.45)	0.408	63.10 (50.70–75.55)	69.30 (54.40–88.70)	0.007	0.026	0.821
Creatine kinase, units/L	86.50 (51.25–161.00)	87.90 (47.00–152.00)	0.506	61.50 (42.00–92.75)	74.50 (50.50–130.25)	0.003	<0.001	0.875
Glucose, mmol/L	5.31 (4.85–6.40)	8.98 (6.43–12.19)	<0.001	5.14 (4.62–6.00)	8.88 (6.23–12.11)	<0.001	0.002	0.894
HbA_{1c}, %	5.90 (5.38–6.33)	7.30 (6.80–9.03)	<0.001	5.90 (5.70–6.20)	8.30 (7.30–9.50)	<0.001	0.793	0.167
HbA_{1c}, mmol/mol	41.00 (35.00–46.00)	56.00 (51.00–75.00)		41.00 (39.00–44.00)	67.00 (56.00–80.00)			
Infection-related indices								
CRP, mg/dL	1.74 (0.24–4.28)	2.51 (0.37–5.16)	0.287	0.49 (0.08–2.81)	2.86 (0.55–5.39)	<0.001	<0.001	0.828
IL-6, pg/mL	4.97 (1.95–29.02)	10.10 (4.07–34.77)	0.128	2.86 (1.73–6.59)	5.55 (2.97–15.67)	0.011	0.004	0.240
Procalcitonin, ng/mL	0.06 (0.04–0.11)	0.06 (0.04–0.19)	0.240	0.05 (0.04–0.07)	0.07 (0.05–0.14)	<0.001	<0.001	0.760
ESR, mm/h	37.00 (16.00–59.00)	43.50 (25.50–61.00)	0.130	25.00 (12.50–48.00)	59.50 (23.50–85.25)	<0.001	0.018	0.308
Coagulation function								
APTT, s	28.80 (25.50–32.30)	28.85 (24.3–34.18)	0.720	27.90 (24.80–31.10)	27.50 (23.60–30.70)	0.303	0.005	0.197
PT, s	11.50 (10.90–12.20)	11.65 (10.90–12.60)	0.279	11.50 (11.00–12.00)	11.60 (11.00–12.30)	0.233	0.706	0.689
D-dimer, mg/L	0.50 (0.23–1.15)	0.72 (0.48–2.18)	0.001	0.50 (0.23–1.22)	0.98 (0.42–2.39)	<0.001	0.834	0.954

Data are n (%) or median (IQR) unless otherwise indicated. Data were collected on admission, except for clinical outcomes. ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ESR, erythrocyte sedimentation rate; LOS, length of stay; PT, prothrombin time. *Cases with diabetes vs. those without diabetes. †Confirmed COVID-19 cases vs. clinically diagnosed COVID-19 cases.

risk factors related to either in-hospital death or poor prognosis in all patients (Table 3).

Characteristics of Glucose-Lowering Medicine Users

Of the 120 patients with COVID-19 and diabetes with available glucose-lowering medication history, insulin users presented some laboratory indices that were significantly different from the indices of those who did not use insulin, including lower albumin, higher infection-related indices (CRP, procalcitonin, and erythrocyte sedimentation rate), and higher blood glucose and HbA_{1c} on admission (Table 4). When comparing insulin users with non–insulin users among those with confirmed COVID-19, increases in CRP and procalcitonin remained statistically significant (Supplementary Table 4). However, the insulin and no-insulin groups showed no significant difference in the percentages of those with severe and critical illness on admission (16.90% [12 patients] in the insulin group vs. 10.20% [5 patients] in

Table 3—Univariable and multivariable logistic regression for risk factors associated with in-hospital death and poor prognosis in all patients with COVID-19 and in patients with diabetes and COVID-19

	All patients				Patients with diabetes			
	Risk factors associated with in-hospital death		Risk factors associated with poor prognosis*		Risk factors associated with in-hospital death		Risk factors associated with poor prognosis*	
	Univariable OR (95% CI)	*P* value	Univariable OR (95% CI)	*P* value	Univariable OR (95% CI)	*P* value	Univariable OR (95% CI)	*P* value
Age, years	1.10 (1.08, 1.12)	<0.001	1.04 (1.03, 1.05)	<0.001	1.08 (1.03, 1.13)	0.001	1.03 (1.00, 1.06)	0.103
Sex, female vs. male	0.38 (0.24, 0.61)	<0.001	0.46 (0.35, 0.60)	<0.001	0.40 (0.16, 0.96)	0.041	0.36 (0.17, 0.77)	0.009
Diabetes	2.51 (1.53, 4.13)	<0.001	2.21 (1.50, 3.26)	<0.001	NA†	NA†	NA†	NA†
Hypertension	3.48 (2.24, 5.40)	<0.001	2.50 (1.86, 3.37)	<0.001	1.21 (0.50, 2.96)	0.673	1.25 (0.60, 2.61)	0.554
Cardiovascular disease	8.29 (5.02, 13.68)	<0.001	3.63 (2.17, 6.07)	<0.001	3.75 (1.48, 9.48)	0.005	3.59 (1.16, 11.06)	0.026
Chronic kidney disease	13.91 (7.23, 26.80)	<0.001	7.23 (2.82, 18.57)	<0.001	4.14 (1.37, 12.45)	0.012	8.08 (1.03, 63.29)	0.047
Chronic lung disease	4.38 (1.74, 11.03)	0.002	2.48 (0.96, 6.40)	0.060	NA‡	NA‡	NA‡	NA‡
Nervous system disease	19.14 (10.38, 35.30)	<0.001	7.63 (3.23, 18.06)	<0.001	10.79 (3.62, 32.14)	<0.001	9.40 (1.21, 73.10)	0.032
White blood cells, $\times 10^9$/L	1.17 (1.10, 1.25)	<0.001	1.10 (1.04, 1.16)	<0.001	1.39 (1.17, 1.65)	<0.001	1.07 (0.945, 1.23)	0.319
Neutrophils, $\times 10^9$/L	1.26 (1.19, 1.34)	<0.001	1.17 (1.10, 1.24)	<0.001	1.42 (1.19, 1.69)	<0.001	1.15 (0.97, 1.35)	0.105
Lymphocytes, $\times 10^9$/L	0.27 (0.17, 0.44)	<0.001	0.42 (0.34, 0.54)	<0.001	0.78 (0.37, 1.65)	0.520	0.48 (0.26, 0.86)	0.015
Albumin, g/L	0.82 (0.78, 0.86)	<0.001	0.91 (0.88, 0.93)	<0.001	0.91 (0.83, 1.00)	0.057	0.88 (0.80, 1.00)	0.003
ALT, units/L	1.00 (1.00, 1.00)	0.179	1.00 (1.00, 1.00)	0.404	1.00 (0.95, 1.01)	0.194	1.00 (0.98, 1.01)	0.603
AST, units/L	1.01 (1.00, 1.02)	0.031	1.01 (1.01, 1.02)	<0.001	1.01 (0.98, 1.03)	0.592	1.01 (0.98, 1.03)	0.657
LDH, units/L	1.00 (1.00, 1.01)	<0.001	1.01 (1.01, 1.01)	<0.001	1.00 (1.00, 1.01)	0.034	1.00 (1.00, 1.01)	0.248
Urea, mmol/L	1.16 (1.11, 1.21)	<0.001	1.14 (1.08, 1.21)	<0.001	1.07 (1.01, 1.14)	0.034	1.25 (1.07, 1.46)	0.005
Creatinine, μmol/L	1.00 (1.00, 1.00)	<0.001	1.01 (1.00, 1.01)	0.011	1.00 (1.00, 1.00)	0.613	1.01 (1.00, 1.02)	0.056
Creatine kinase, units/L	1.00 (1.00, 1.00)	0.014	1.00 (1.00, 1.00)	0.058	1.00 (1.00, 1.01)	0.325	1.00 (1.00, 1.00)	0.764
Glucose, mmol/L	1.16 (1.09, 1.24)	<0.001	1.17 (1.10, 1.25)	<0.001	1.05 (0.97, 1.14)	0.257	1.04 (0.96, 1.13)	0.330
CRP, mg/dL	1.22 (1.16, 1.28)	<0.001	1.29 (1.22, 1.37)	<0.001	1.02 (1.01, 1.04)	0.013	1.01 (0.99, 1.03)	0.324
D-dimer, mg/L	1.02 (1.01, 1.04)	0.007	1.06 (1.01, 1.10)	0.008	1.00 (0.97, 1.03)	0.852	1.00 (0.98, 1.03)	0.789
	Multivariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age, years	1.09 (1.07, 1.12)	<0.001	1.02 (1.01, 1.03)	<0.001	1.09 (1.04, 1.15)	0.001	1.02 (0.99, 1.05)	0.249
Albumin, g/L	0.91 (0.86, 0.97)	0.006	0.98 (0.95, 1.02)	0.302	0.94 (0.84, 1.05)	0.288	0.91 (0.83, 0.99)	0.030
Creatinine, μmol/L	1.00 (1.00, 1.00)	0.001	1.00 (1.00, 1.01)	0.064	1.00 (1.00, 1.00)	0.468	1.01 (1.00, 1.02)	0.154
CRP, mg/dL	1.14 (1.08, 1.21)	<0.001	1.20 (1.13, 1.28)	<0.001	1.12 (1.00, 1.24)	0.043	1.16 (1.01, 1.32)	0.033
Glucose, mmol/L	1.08 (1.01, 1.16)	0.033	1.06 (1.00, 1.13)	0.072	1.07 (0.97, 1.17)	0.181	1.06 (0.96, 1.17)	0.242

Among all patients with COVID-19, 92 (26 of whom had diabetes) died in the hospital; 473 (93 of whom had diabetes) had a poor prognosis. Laboratory findings tested in no more than half of the total cases were not included in regression models in order to avoid possible bias. Age, albumin, creatinine, CRP, and glucose were chosen as variables for the multivariate analysis of all patients with COVID-19 and all patients with diabetes and COVID-19. $P < 0.05$ was considered significant. ALT, alanine aminotransferase; NA, not available. *Poor prognosis included progression to severe or critical illness, and in-hospital death. †No available result because diabetes is not included in the regression model for patients with diabetes and COVID-19. ‡No available result because only two patients with diabetes had chronic lung disease.

the no-insulin group; $P = 0.426$). Metformin users showed overall higher albumin and lower urea and interleukin-6 (IL-6) on admission than non–metformin users (Table 4). In addition, less malignant initial clinical indices, including a significantly lower white blood cell count, fewer neutrophils, and lower creatine kinase, CRP, and IL-6, were seen in those who use secretagogues than in those who do not (Supplementary Table 5). For users of α-glycosidase or DPP-4 inhibitors, their laboratory findings and clinical outcomes were similar to those of respective nonusers (Supplementary Table 5).

Multivariable regression was performed in order to explore the association of specific glucose-lowering medications with in-hospital death and poor prognosis. Each type of medication was analyzed within a corresponding multivariable regression model (Supplementary Table 6). Compared with non–insulin users, insulin users had a greater risk of poor prognosis (aOR 3.58 [95% CI 1.37, 9.35]; $P = 0.009$). However, multivariable regression analyses indicated that none of the glucose-lowering medications (metformin, insulin, α-glycosidase, secretagogues, or DPP-4 inhibitors) were associated with in-hospital death (Supplementary Table 6).

Comorbid Hypertension in Blood Pressure–Lowering Drug Users

Of the patients with diabetes and COVID-19, 71 had comorbid hypertension and available blood pressure–lowering medication history (Supplementary Table 7). Among them, 32 used an ACE inhibitor (ACEI) or angiotensin II type-I receptor blocker (ARB), which were reported to increase the expression of ACE2 (14), a crucial target of SARS-CoV-2 (15). No significant difference was present between the clinical outcomes within the ACEI/ARB group and those within the no-ACEI/ARB group (Supplementary Table 7).

Table 4—Clinical characteristics, outcomes, and laboratory findings according to medication (metformin and insulin) use

	Patients with COVID-19 and diabetes (n = 120)					
	Taking metformin (n = 43)	Not taking metformin (n = 77)	P value*	Taking insulin (n = 71)	Not taking insulin (n = 49)	P value†
Baseline characteristics and clinical outcomes						
Age, years	62.0 (56.0–69.0)	67.0 (57.5–73.0)	0.082	65.0 (57.0–72.0)	65.0 (56.0–73.0)	0.943
Hospital LOS, days	24.0 (16.0–33.0)	23.0 (17.0–33.0)	0.928	25.0 (19.0–35.0)	19.0 (13.0–30.5)	0.018
In-hospital death	4 (9.30%)	15 (19.48%)	0.194	16 (22.54%)	3 (6.12%)	0.021
Poor prognosis	30 (69.77%)	50 (64.94%)	0.688	58 (81.69%)	22 (44.90%)	<0.001
Laboratory findings						
Hematologic, $\times 10^9$/L						
White blood cells	5.48 (4.43–7.15)	5.52 (4.49–7.31)	0.749	5.64 (4.41–7.45)	5.21 (4.54–7.16)	0.370
Neutrophils	3.98 (2.74–5.54)	3.83 (2.89–5.41)	0.622	4.06 (3.12–5.56)	3.4 (2.67–4.98)	0.092
Lymphocytes	1.02 (0.64–1.36)	0.96 (0.67–1.53)	0.887	0.88 (0.64–1.38)	1.15 (0.69–1.57)	0.092
Monocytes	0.32 (0.23–0.48)	0.39 (0.27–0.55)	0.114	0.35 (0.26–0.54)	0.36 (0.24–0.53)	0.711
Platelets	196.00 (139.00–225.00)	182.00 (146.00–237.00)	0.948	182.00 (139.00–224.00)	188.00 (162.50–257.50)	0.160
Biochemical						
Hemoglobin, g/L	124.00 (113.00–140.00)	123.00 (112.00–131.00)	0.349	125.00 (106.00–138.00)	123.00 (113.50–133.00)	0.796
Albumin, g/L	38.60 (34.90–41.80)	36.70 (33.10–39.35)	0.039	35.80 (32.40–39.30)	38.40 (35.25–41.50)	0.007
Total bilirubin, μmol/L	10.00 (8.60–14.10)	8.80 (6.00–13.30)	0.206	9.20 (6.10–11.90)	9.90 (7.70–14.45)	0.149
ALT, units/L	19.90 (13.00–27.20)	19.30 (12.05–32.70)	0.696	19.30 (12.00–31.80)	19.70 (15.00–32.15)	0.223
AST, units/L	18.50 (15.10–35.50)	23.30 (15.25–31.95)	0.644	23.90 (15.60–33.00)	19.00 (13.80–31.45)	0.423
LDH, units/L	190.50 (158.25–238.50)	201.00 (164.00–265.00)	0.440	199.00 (164.00–265.00)	192.00 (151.25–254.50)	0.403
Urea, mmol/L	4.58 (3.69–6.04)	5.90 (3.98–8.15)	0.031	5.85 (3.85–10.06)	4.89 (3.73–6.37)	0.052
Creatinine, μmol/L	67.30 (53.70–84.90)	70.60 (55.15–98.60)	0.315	70.50 (55.60–116.10)	67.30 (51.70–85.75)	0.215
Creatine kinase, units/L	74.00 (47.25–116.50)	77.90 (50.90–152.00)	0.268	90.20 (49.00–147.00)	61.50 (47.25–114.5)	0.132
Glucose, mmol/L	9.44 (7.16–12.07)	9.60 (6.69–12.62)	0.795	9.80 (7.22–14.37)	8.67 (6.37–11.03)	0.020
HbA_{1c}, %	7.70 (6.90–9.13)	8.40 (7.35–10.65)	0.186	8.80 (7.40–10.85)	7.50 (6.80–8.25)	0.023
HbA_{1c}, mmol/mol	61.00 (52.00–76.00)	68.00 (57.00–93.00)		73.00 (57.00–96.00)	58.00 (51.00–67.00)	
Infection-related indices						
CRP, mg/dL	1.79 (0.19–4.29)	2.83 (0.75–5.44)	0.124	3.45 (1.18–6.88)	0.79 (0.14–3.45)	<0.001
IL-6, pg/mL	4.07 (2.37–10.28)	11.10 (3.70–62.88)	0.020	10.10 (3.20–59.10)	4.30 (2.99–11.49)	0.255
Procalcitonin, ng/mL	0.06 (0.04–0.09)	0.08 (0.05–0.17)	0.070	0.08 (0.05–0.24)	0.05 (0.04–0.08)	<0.001
ESR, mm/h	39.00 (22.00–80.75)	48.00 (28.50–78.00)	0.433	52.00 (30.50–88.00)	37.00 (20.00–64.00)	0.034
Coagulation function						
APTT, s	26.30 (23.03–30.05)	28.20 (24.10–31.90)	0.272	28.20 (24.30–33.10)	26.60 (23.10–30.00)	0.144
PT, s	11.45 (10.88–11.95)	11.50 (11.00–12.60)	0.240	11.70 (10.90–12.60)	11.30 (10.90–11.90)	0.105
D-dimer, mg/L	0.77 (0.35–2.22)	0.83 (0.46–2.31)	0.447	0.89 (0.43–1.73)	0.77 (0.43–2.54)	0.752

Data are n (%) or median (IQR) unless otherwise indicated. Data were collected at admission, except for clinical outcomes. ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ESR, erythrocyte sedimentation rate; PT, prothrombin time. *Patients who take metformin vs. those who do not. †Patients who take insulin vs. those who do not.

CONCLUSIONS

Facing COVID-19, individuals with diabetes are at risk for greater susceptibility to infection with worse outcomes (2,6,16). However, little is known about the clinical characteristics of patients with COVID-19 and comorbid diabetes, and little prevention and treatment guidance exists for patients with diabetes who are infected with SARS-CoV-2. This study aims to describe the clinical characteristics and outcomes in patients with diabetes and COVID-19, sex effects, and use of glucose-lowering or blood pressure–lowering medication.

Characteristics of Patients With Diabetes Who Have COVID-19

Overall higher mortality and poorer prognosis were seen in patients with confirmed COVID-19 than in clinically diagnosed cases (Table 1). For patients without diabetes, those with confirmed COVID-19 showed more malignant initial laboratory indices than those with clinically diagnosed COVID-19. However, there was no significant difference in the initial laboratory findings in patients with diabetes who had confirmed COVID-19 and those who had clinically diagnosed COVID-19 (Table 2). In our study population, the proportions of confirmed COVID-19 cases were similar between people with and people without diabetes. We therefore deduce that the basic conditions of patients with COVID-19 with comorbid diabetes were similar among the confirmed and clinically diagnosed cases, and were worse overall than in those without diabetes.

As is well known, patients with diabetes are highly susceptible to infection (16,17). Indeed, diabetes is an important risk factor for morbidity and mortality in patients infected with other coronaviruses such as SARS-CoV (18,19) and Middle East respiratory syndrome–related coronavirus (20,21). Our findings indicated that more fatalities occurred among patients with diabetes and COVID-19 than in those with COVID-19 but without diabetes, which was consistent with the results of another study (6).

Hypertension, the leading comorbidity of COVID-19 (Table 1), was more prevalent in patients with COVID-19 and diabetes than in those with the infection but without diabetes (Table 2). Analysis of laboratory indices of patients with COVID-19 indicated that, compared to patients without diabetes, patients with diabetes presented more severe inflammatory responses, acute kidney injury,

and secondary infection (Table 2). Together, these findings support that patients with diabetes are more vulnerable to COVID-19 infection.

Risk Factors for Patients With Diabetes and COVID-19

Our data suggest that older patients with diabetes are at greater risk for mortality (Table 3). In addition, although hypertension was the most common comorbidity in patients with diabetes and COVID-19 (Table 2), it had no association with their poor outcomes (Table 3). Death rates were higher among patients with COVID-19 who had diabetes than in those without diabetes (Table 2), and univariable regression analyses showed that diabetes increased the odds of in-hospital death and poor prognosis for all patients (Table 3). Because including two highly correlated variables such as glucose and diabetes in the same model can make it difficult to interpret their coefficients, glucose was included in the multivariable regression models. High blood glucose was also an independent risk factor for mortality in patients with COVID-19 in this cohort, as demonstrated by multivariable regression analyses (Table 3).

The only independent risk factor for either mortality or poor prognosis in patients with COVID-19 and diabetes was CRP (Table 3), a typical infection-related protein that not only indicates secondary infection but also links inflammation and chronic diseases including diabetes (22). Consistently, previous studies reported that the association between diabetes and lung dysfunction (23,24) may be partly explained by systemic inflammation (25,26). Therefore, concerns about secondary infection and inflammatory responses are necessary when clinically managing patients with diabetes who have COVID-19.

Impact of Various Glucose-Lowering and Blood Pressure–Lowering Medications

Insulin users showed worse clinical outcomes and some more malignant initial laboratory findings than those who did not use insulin (Table 4). In this cohort, multivariable regression analysis further indicated a greater risk of COVID19-related poor prognosis in patients with diabetes who use insulin and have COVID-19 (Supplementary Table 6). Considering a recent proposal that insulin is preferred for controlling hyperglycemia in hospitalized patients with diabetes who have COVID-19 (27), more evidence from clinical practice is warranted in order to identify the impact of different glucose-lowering medications on patients with diabetes who have COVID-19, and more attention should be paid to insulin users.

A recent hypothesis has proposed that the increased risk for SARS-CoV-2 infection among patients with diabetes or hypertension may be due to the substantially elevated expression of ACE2 in those treated with ACEI/ARB drugs (14,15,28). In this study, hypertension accounts for the largest proportion of comorbidities, and ACEI/ARB medications were mostly used against hypertension. However, comparisons of the clinical characteristics and outcomes of ACEI/ARB users with those of non–ACEI/ARB users among the patients with comorbid diabetes and hypertension showed no significant differences (Supplementary Table 7).

Study Limitations

Our study has limitations in classifying true SARS-CoV-2-negative cases. Although clinically diagnosed patients showed symptoms and biochemical indices similar to those of patients with confirmed COVID-19, we cannot rule out the possible existence of truly uninfected patients among the clinically diagnosed cases.

Conclusion

Among those with COVID-19, compared with patients without diabetes, patients with comorbid diabetes showed aggravated kidney injury and severe inflammatory response. In those with confirmed COVID-19, the percentage of comorbid nervous system disease was significantly higher among women with diabetes than in women without diabetes. For patients with diabetes and COVID-19, increasing odds of in-hospital death were associated with older age and elevated CRP, whereas risk factors for poor prognosis were lower albumin and higher CRP. Insulin usage was associated with poor prognosis, suggesting that more attention is needed regarding patients with COVID-19 who have diabetes and use insulin. Although the results were based on a small sample size, neither comorbid hypertension nor ACEI/ARB medication use had a significant impact on clinical outcomes of patients with diabetes and COVID-19.

Funding. This work was supported by the National Key R&D Program of China (grants 2019YFA0802701 and 2018YFA0800700), the National Natural Science Foundation of China (grants 91957114, 31971066, 31871381, and 31671195), and the Family Planning Commission of Wuhan (grant WX18M02).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors contributed to this study. L.Z. and K.H. conceived and designed the study. Y.C., D.Y., B.C., J.C., A.P., and A.D. acquired data. Y.C., D.Y., B.C., J.C., C.Y., C.L., M.X., and Y.Z. analyzed and interpreted data. Y.C., D.Y., B.C., L.Z., and K.H. wrote the article and revised it critically. K.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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