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ABOUT COVER

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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ORIGINAL ARTICLE

Retrospective Study

Diabetes patients with comorbidities had unfavorable outcomes following COVID-19: A retrospective study

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Author contributions: Lu HY and Mei J conceptualized the design of the study, had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; Luo SK and Hu WH drafted the manuscript; Lu ZJ, Luo SK did the analysis, Fan YM reviewed the statistical methods; Li C, Chen QJ, Chen ZS, Fan YM collected the data; Lu ZJ, Ye JF, Chen SY, Wang LL and Tong JL recorded the data.

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Abstract

BACKGROUND

Previous studies have shown that diabetes mellitus is a common comorbidity of coronavirus disease 2019 (COVID-19), but the effects of diabetes or anti-diabetic

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Institutional review board statement: This case series' study was approved by institutional Ethics Commission of Ningbo First Hospital of Zhejiang University, institutional Ethics Commission of Hubei No. 3 People's Hospital of Jianghan University, institutional Ethics Commission of People's Hospital of Jiayu County, institutional Ethics Commission of the First Hospital of Jingzhou.

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medication on the mortality of COVID-19 have not been well described.

AIM

To investigate the outcome of different statuses (with or without comorbidity) and anti-diabetic medication use before admission of diabetic after COVID-19.

METHODS

In this multicenter and retrospective study, we enrolled 1422 consecutive hospitalized patients from January 21, 2020, to March 25, 2020, at six hospitals in Hubei Province, China. The primary endpoint was in-hospital mortality. Epidemiological material, demographic information, clinical data, laboratory parameters, radiographic characteristics, treatment and outcome were extracted from electronic medical records using a standardized data collection form. Most of the laboratory data except fasting plasma glucose (FPG) were obtained in first hospitalization, and FPG was collected in the next day morning. Major clinical symptoms, vital signs at admission and comorbidities were collected. The treatment data included not only COVID-19 but also diabetes mellitus. The duration from the onset of symptoms to admission, illness severity, intensive care unit (ICU) admission, and length of hospital stay were also recorded. All data were checked by a team of sophisticated physicians.

RESULTS

Patients with diabetes were 10 years older than non-diabetic patients [(39 - 64) *vs* (56 - 70), $P < 0.001$] and had a higher prevalence of comorbidities such as hypertension (55.5% *vs* 21.4%, $P < 0.001$), coronary heart disease (CHD) (9.9% *vs* 3.5%, $P < 0.001$), cerebrovascular disease (CVD) (3% *vs* 2.2%, $P < 0.001$), and chronic kidney disease (CKD) (4.7% *vs* 1.5%, $P = 0.007$). Mortality (13.6% *vs* 7.2%, $P = 0.003$) was more prevalent among the diabetes group. Further analysis revealed that patients with diabetes who took acarbose had a lower mortality rate (2.2% *vs* 26.1, $P < 0.01$). Multivariable Cox regression showed that male sex [hazard ratio (HR) 2.59 (1.68 - 3.99), $P < 0.001$], hypertension [HR 1.75 (1.18 - 2.60), $P = 0.006$), CKD [HR 4.55 (2.52-8.20), $P < 0.001$], CVD [HR 2.35 (1.27 - 4.33), $P = 0.006$], and age were risk factors for the COVID-19 mortality. Higher HRs were noted in those aged ≥ 65 (HR 11.8 [4.6 - 30.2], $P < 0.001$) *vs* 50-64 years (HR 5.86 [2.27 - 15.12], $P < 0.001$). The survival curve revealed that, compared with the diabetes only group, the mortality was increased in the diabetes with comorbidities group ($P = 0.009$) but was not significantly different from the non-comorbidity group ($P = 0.59$).

CONCLUSION

Patients with diabetes had worse outcomes when suffering from COVID-19; however, the outcome was not associated with diabetes itself but with comorbidities. Furthermore, acarbose could reduce the mortality in diabetic.

Key Words: Diabetes; Coronavirus disease 2019; Mortality; Risk factors; Acarbose

Core Tip: Previous studies have shown that diabetes mellitus is a common comorbidity of coronavirus disease 2019 (COVID-19), but the effects of diabetes or antidiabetic medication on the mortality of COVID-19 have not been well described. This retrospective and multiple-center study investigate the outcome of different statuses (with or without comorbidity) and antidiabetic medication use before admission of diabetic after COVID-19.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become an ongoing pandemic and has caused considerable mortality worldwide[1]. Diabetes is a common comorbidity, especially in elderly patients, but the effects of diabetes or anti-diabetic medication on the severity and mortality of COVID-19 have not been well described. As of April 27, 2021, nearly 150 million COVID-19 cases had been confirmed around the world, and more than 3 million patients died of COVID-19 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Well-controlled blood glucose (3.9-10.0 mmol/L) in preexisting diabetes was associated with a significant reduction in the composite adverse outcomes and death of patients with COVID-19[2]. Patients with diabetes often have several comorbidities, and previous research has revealed that hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), cardiovascular disease and cerebrovascular disease (CVD) are also associated with worse outcomes in patients suffering from COVID-19[3-6]. However, few studies have described the outcome of different comorbidity statuses of patients with diabetes after infection with COVID-19. In addition, few studies have focused on whether anti-diabetic medication would influence the outcome of patients with preexisting diabetes who suffer from COVID-19. Considering this, we performed a multicenter study to investigate the outcome of different statuses (with or without comorbidity) and anti-diabetic medication before admission of patients with diabetes with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

MATERIALS AND METHODS

Study design and participants

This is a multicenter, observational, retrospective, real-world study that included adult inpatients from six designated tertiary centers (Supplementary Table 1) between January 21 and March 25, 2020. A total of 1422 patients with COVID-19 were screened for this study (Figure 1). All patients were diagnosed with COVID-19 in accordance with WHO interim guidance.

Data collection

Epidemiological material, demographic information, clinical data, laboratory parameters, radiographic characteristics, treatment and outcome were extracted from electronic medical records using a standardized data collection form. Most of the laboratory data except fasting plasma glucose (FPG) were obtained in first hospitalization, and FPG was collected in the next day morning. Major clinical symptoms, vital signs at admission and comorbidities were collected. The treatment data included not only COVID-19 but also diabetes mellitus. The duration from the onset of symptoms to admission, illness severity, intensive care unit (ICU) admission, and length of hospital stay were also recorded. All data were checked by a team of sophisticated physicians.

Diabetes was defined as a history record of diabetes and the use of anti-diabetic medication; otherwise, newly diagnosed diabetes was based on the level of fasting plasma glucose (FPG) (≥ 7.0 mmol/L), random plasma glucose (≥ 11.1 mmol/L), glycosylated hemoglobin (HbA1c) ≥ 6.5% and classic symptoms of hyperglycemia during hospital stay (as the oral glucose tolerance test may lead to hyperglycemia and then to worsening of a COVID-19 patient's illness, it was not used for diagnosis of diabetes in our study[7]). Hypertension was defined by a history of hypertension, the use of anti-hypertensive drugs, or the National Heart Lung and Blood Institute criteria [8]. Coronary heart disease was defined by a history of coronary heart disease. CVD was defined by a history of CVD. ARDS was defined according to the Berlin definition [9]. Acute kidney injury (AKI) was diagnosed according to the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines[10]. Acute cardiac injury (ACI) was reported if serum levels of myocardial injury biomarkers were higher than the upper limit of normal[2]. The criteria for classification of COVID-19 severity were according to the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 8)[11]. We divided the patients into two groups: the non-severe group (mild and general types) and the severe group (severe and critical types).

Outcomes

The primary outcome was all-cause mortality after admission. Secondary outcomes were ICU admission and incidence of SARS-CoV-2-related complications, including ARDS, AKI, ACI, secondary infection, shock and hypoproteinemia.

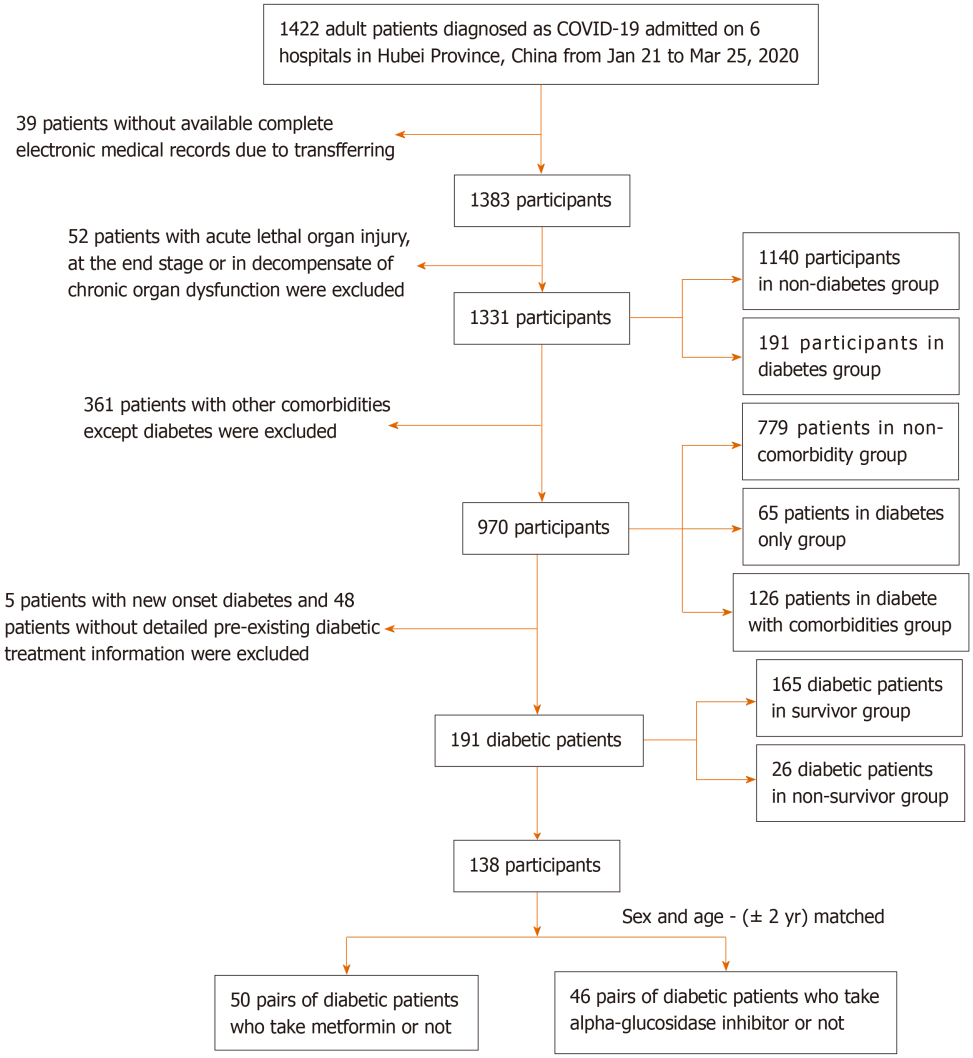

Figure 1 Flow chart of patient recruitment. COVID-19: Coronavirus disease 2019.

Statistical analysis

Continuous variables were described as the mean ± SD or median (IQR). Categorical variables were calculated as frequencies and percentages with available data. The differences in continuous variables among groups were assessed using the independent sample *t*-test or one-way ANOVA for normally distributed continuous variables or the Mann-Whitney *U* test or Kruskal-Wallis *H* test for skewed continuous variables. Pearson's χ^2 test and Fisher's exact test were performed for unordered categorical variables. The Mann-Whitney *U* test or the Kruskal-Wallis *H* test was used for ordered categorical variables. To explore the risk factors associated with mortality, multivariable Cox regression models were performed. The Kaplan-Meier plot was performed to compare the survival probability for the diabetes and non-diabetes groups and among the patients with no comorbidities, only diabetes and diabetes with comorbidities by log-rank test. Additionally, we did not process the missing data. The statistical analyses were conducted with SPSS (version 25.0). A two-sided *P* value less than 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Yameng Fan from Wuhan University.

RESULTS

Clinical characteristics and laboratory results of 1331 patients with COVID-19 divided into different groups

The characteristics of this study population at baseline are given in Table 1. The median age was 54 years old (39-64) and 64 years old (56-70) in the non-diabetes and

Table 1 Baseline characteristics of 1331 coronavirus disease 2019 patients divided into different groups

	Total (*n* = 1331)	Non-diabetes (*n* = 1140)	Diabetes (*n* = 191)	*P*[1] value	Non-comorbidity (*n* = 779)	Diabetes only (*n* = 65)	Diabetes with comorbidities (*n* = 126)	*P*[2] value
Demographic								
Male	673 (50.6)	565 (49.6)	108 (56.5)	0.074	369 (47.4)	40 (61.5)	68 (54.0)	0.046
Age, yr	56.0 (42.0-65.0)	54.0 (39.0-64.0)	64.0 (56.0-70.0)	< 0.001	48.0[c] (36.0-60.0)	57.0 (50.0-64.0)	67.0[c] (59.0-72.0)	< 0.001
18-49	500(37.6)	477 (41.8)	23 (12.0)	<0.001	415 (53.3)[c]	16 (24.6)	7 (5.6)[c]	< 0.001[d]
50-64	458 (34.4)	382 (33.5)	76 (39.8)		253 (32.5)	34 (52.3)	42 (33.3)	
≥ 65	373 (28.0)	281 (24.6)	92 (48.2)		111 (14.2)	15 (23.1)	77 (61.1)	
Wuhan exposure	1190 (89.4)	1008 (88.4)	182 (95.3)	0.004	686 (88.3)	61 (95.3)	120 (95.2)	0.018
Current smoking	107 (8.1)	93 (8.2)	14 (7.4)	0.736	55 (7.2)	3 (4.7)	11 (8.9)	0.149
Onset of symptom, d	8.0 (5.0-14.0)	8.0 (5.0-14.0)	10.0 (6.0-13.0)	0.217	8.0 (4.8-14.0)	10.0 (6.5-16.5)	10.0 (5.8-12.0)	0.109
Symptoms								
Fever	955 (71.8)	823 (72.2)	132 (69.1)	0.381	570 (73.2)	46 (70.8)	86 (68.3)	0.496
Dyspnea	270 (20.3)	227 (19.9)	43 (22.5)	0.408	135 (17.3)	9 (13.8)	34 (27.0)	0.021
Cough	777 (58.4)	660 (57.9)	117 (61.3)	0.383	433 (55.6)	46 (70.8)	71 (56.7)	0.060
Sputum production	138 (10.4)	126 (11.1)	12 (6.3)	0.045	84 (10.8)	4 (6.2)	8 (6.3)	0.175
Hemoptysis	3 (0.2)	3 (0.3)	0 (0.0)	1.000	1 (0.1)	0 (0.0)	0 (0.0)	0.885
Fatigue	362 (27.2)	306 (26.8)	56 (29.3)	0.476	212 (27.2)	16 (24.6)	40 (31.7)	0.489
Headache	47 (3.5)	44 (3.9)	3 (1.6)	0.169	29 (3.7)	3 (4.6)	0 (0.0)	0.010
Nausea or vomiting	44 (3.3)	39 (3.4)	5 (2.6)	0.566	25 (3.2)	2 (3.1)	3 (2.4)	0.939
Diarrhea	112 (8.4)	97 (8.5)	15 (7.9)	0.763	63 (8.1)	9 (13.8)	6 (4.8)	0.091
Temperature, °C	36.8 (36.5-37.5)	36.8 (36.5-37.5)	36.7 (36.4-37.4)	0.018	36.8 (36.5-37.5)	36.8 (36.5-37.6)	36.6 (36.4-37.3)	0.018
≥ 39	30 (2.4)	25 (2.3)	5 (2.7)	0.980	16 (2.2)	2 (3.1)	3 (2.4)	0.889
Pulse ≥ 100 beats per min	244 (18.5)	209 (18.5)	35 (18.3)	0.955	125 (16.1)	12 (18.5)	23 (18.30)	0.761
Blood oxygen saturation < 93%	124 (11.1)	92 (9.6)	32 (19.8)	< 0.001	43 (6.5)	7 (12.5)	25 (23.6)	< 0.001
Respiratory rate > 24 breaths/min	71 (5.4)	56 (5.0)	15 (7.9)	0.105	27 (3.5)	2 (3.1)	13 (10.3)	0.002
Mean systolic blood pressure, mmHg	125 (120-135)	124 (119-135)	128 (120-140)	0.001	121 (118-131)	127 (120-133)	130 (120-140)	< 0.001
Mean diastolic blood pressure, mmHg	80.0 (74.0-85.0)	80.0 (74.0-85.0)	80.0 (74.0-85.0)	0.777	80.0 (73.0-83.0)	80.0 (72.5-85.0)	80.0 (74.0-84.3)	0.550
Radiological findings								
Ground glass opacity	294 (22.1)	265 (23.2)	29 (15.2)	0.013	195 (25.0)	9 (13.8)	20 (15.9)	0.014
Bilateral patchy shadowing	813 (61.1)	687 (60.3)	126 (66.0)	0.134	62 (8.0)	5 (7.7)	4 (3.2)	0.107
Bilateral lesions	962 (82.1)	805 (80.1)	157 (94.0)	< 0.001	524 (76.2)[a]	53 (91.4)	104 (95.4)	< 0.001
Comorbidity								
Hypertension	350 (26.3)	244 (21.4)	106 (55.5)	< 0.001	-	-	-	-
CHD	59 (4.4)	40 (3.5)	19 (9.9)	< 0.001	-	-	-	-
Chronic liver disease	20 (1.5)	18 (1.6)	2 (1.0)	0.812	-	-	-	-

CVD	39 (2.9)	25 (2.2)	14 (7.3)	< 0.001	-	-	-	-
CKD	26 (2.0)	17 (1.5)	9 (4.7)	0.007	-	-	-	-
COPD	10 (0.8)	10 (0.9)	0 (0.0)	0.397	-	-	-	-

Data are expressed as *n* (%), mean ± SD or median (IQR). *P* values were calculated by *t* Test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test, One-Way ANOVA or Kruskal-Wallis *H* test as appropriate.
[1]Comparing groups of diabetes and non-diabetes patients.
[2]Comparing groups of non-comorbidity, only diabetes and diabetes with comorbidities.
[d]Mann-Whitney *U* test comparing all subcategories. Compared with diabetes only group.
[a]$P < 0.05$.
[b]$P < 0.05$.
[c]$P < 0.001$.
CHD: Coronary heart disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary diseas; CVD: Cerebrovascular diseasee.

diabetes groups, respectively. Comorbidities such as hypertension (55.5% *vs* 21.4%), coronary heart disease (9.9% *vs* 3.5%), CVD (7.3% *vs* 2.2%), and CKD (4.7% *vs* 1.5%) were significantly more prevalent in the diabetes group. Mean systolic blood pressure (SBP) was higher in the diabetes group. Moreover, decreased blood oxygen saturation (lower than 93%) occurred more frequently in the diabetes group *vs* the non-diabetes group (19.8% *vs* 19.6%) on admission. Chest CT scan revealed that the incidence of bilateral lesions was higher (94% *vs* 80.1%) in the diabetes group than in the non-diabetes group.

There were numerous differences in laboratory results between the diabetes group and the non-diabetes group with COVID-19 (Table 2). FPG levels were significantly higher in the diabetes group than in the non-diabetes group, as expected, with higher levels of HbA1c. Patients with diabetes had a higher white blood cell count (WBC), neutrophil count (NEU), neutrophil to lymphocyte ratio (NLR), and C-reactive protein (CRP) and a lower lymphocyte count (LY) than the non-diabetic group. These results revealed that diabetes represented more severe inflammation. The percentage of high levels of prothrombin time (PT) and D-dimer among the diabetes group was higher than that among the non-diabetes group. The serum level of albumin (ALB) was lower in the diabetes group than in the non-diabetes group. Meanwhile, urea nitrogen (BUN), a marker of kidney function, was higher in the diabetes group. Non-diabetes participants had significantly lower serum levels of lactate dehydrogenase. Compared with the non-diabetes group, the diabetes group had higher levels of total cholesterol (TCH) and lower high-density lipoprotein cholesterol (HDL-C).

In addition, a between-group comparison with only the diabetes group was performed. The baseline characteristics and radiological findings are also summarized in Table 1. Patients with diabetes with comorbidities were the oldest among the three groups. There was a significant difference in blood oxygen saturation and respiratory rate among the three groups but no significant differences in the comparison of the non-comorbidity group and only diabetes group or the comparison of the diabetes only group and diabetes with comorbidities group. Chest CT scans indicated that the diabetes only group had more incidences of bilateral lesions than the non-comorbidity group.

Although there were numerous differences in laboratory findings among the non-comorbidity group, diabetes only group and diabetes with comorbidities group (Table 2), only ten items had statistical significance between the non-comorbidity group and diabetes only group, including ALB, sodium, BUN, CRP, and HDL-C, as well as FPG and HbA1c, as expected. These results combined with oxygen saturation indicated that there was no difference in cardiac, liver, lung and coagulation function between the groups.

FPG and HbA1c in the diabetes only group and diabetes with comorbidities group were almost at the same level. Compared with the diabetes only group, the diabetes with comorbidities group had a lower LY and a higher NLR and CRP, which represented a more severe inflammatory response.

Treatment and outcome of 1331 patients with COVID-19 divided into different groups

As shown in Table 3, 1223 of the 1331 patients (91.9%) were discharged from the hospital; the rate of mortality of the diabetes group was higher than that of the non-diabetes group (13.6% *vs* 7.2%). Kaplan-Meier survival analysis for all-cause mortality in patients with COVID-19 is shown in Figure 2. The overall survival rate was significantly lower in the diabetes group (log-rank $P < 0.01$, Figure 2A). Compared

Table 2 Laboratory results of 1331 coronavirus disease 2019 patients divided into different groups

	Total (*n* = 1331)	Non-diabetes (*n* = 1140)	Diabetes (*n* = 191)	*P*[1] value	Non-comorbidity (*n* = 779)	Diabetes only (*n* = 65)	Diabetes with comorbidities (*n* = 126)	*P*[2] value
WBC, × 10^9/L	5.42 (4.18-7.10)	5.35 (4.10-6.95)	5.93 (4.49-7.53)	0.003	5.28 (4.00-6.77)	6.11 (4.27-7.68)	5.85 (4.57-7.32)	0.001
NEUT, × 10^9/L	3.58 (2.53-5.12)	3.45 (2.46-5.07)	4.25 (3.13-5.37)	< 0.001	3.29 (2.33-4.64)	4.16 (2.67-5.40)	4.37 (3.20-5.29)	< 0.001
LY, × 10^9/L	1.15 (0.78-1.59)	1.17 (0.80-1.61)	1.04 (0.72-1.43)	0.015	1.25 (0.86-1.65)	1.27 (0.84-1.73)	0.93 (0.68-1.33)[b]	< 0.001
NLR	2.95 (1.97-5.26)	2.79 (1.88-4.93)	3.84 (2.45-6.37)	< 0.001	2.54 (1.79-4.36)	3.15 (2.08-5.06)	4.29 (2.62-7.30)[a]	< 0.001
Hb, g/L	130 (118-140)	130 (118-140)	120 (117-140)	0.195	131 ± 16.3	132 ± 14.4	125 ± 17.6[b]	< 0.001
PLT, × 10^9/L	196 (150-251)	196 (151-251)	196 (147-255)	0.714	196 (152-242)	197 (147-265)	196 (146-255)	0.974
PCT, ng/mL								
< 0.5	981 (94.4)	838 (94.4)	143 (94.7)	0.869	585 (97.3)	53 (100)	90 (91.8)	0.006
≥ 0.5	58 (5.6)	50 (5.6)	8 (5.3)		16 (2.7)	0 (0.0)	8 (8.2)	
CRP	10.9 (1.7-46.7)	9.1 (1.4-39.0)	29.8 (5.3-75.7)	< 0.001	6.11 (1.0-27.7)[a]	13.2 (3.0-61.5)	39.9 (6.6-77.7)[a]	< 0.001
IL-6, pg/mL	2.77 (1.5-14.09)	2.73 (1.5-13.5)	3.09 (1.5-20.4)	0.471	1.80 (1.50-6.27)	2.32 (1.50-5.06)	4.01 (2.72-28.56)	0.008
PT, s	13.0 (11.3-14.9)	12.9 (11.3-14.6)	14.3 (11.9-15.5)	< 0.001	12.80 (11.20-14.30)	13.70 (10.80-15.05)	14.50 (12.35-16.03)	< 0.001
< 16	830 (85.7)	712 (87.1)	118 (78.1)	0.004	493 (87.7)	41 (83.7)	75 (73.5)	0.001
≥ 16	138 (14.3)	105 (12.9)	33 (21.9)		69 (12.3)	8 (16.3)	27 (26.5)	
D-dimer, mg/L	0.49 (0.26-1.14)	0.46 (0.25-1.10)	0.69 (0.35-1.35)	< 0.001	0.38 (0.23-0.80)	0.46 (0.26-0.91)	0.83 (0.46-1.94)[b]	< 0.001
≤ 0.5	555 (52.5)	497 (55.0)	58 (37.9)	< 0.001	386 (63.4)	27 (50.9)	31 (31.0)[b]	< 0.001[3]
> 0.5 to ≤ 1.0	209 (19.8)	163 (18.0)	46 (30.1)		100 (16.4)	18 (34.0)	28 (28.0)	
> 1.0	293 (27.7)	244 (27.0)	49 (32.0)		123 (20.2)	8 (15.1)	41 (41.0)	
ALB, g/L	38.1 ± 5.8	38.5 ± 5.7	35.7 ± 5.5	< 0.001	39.3 ± 5.9[c]	36.5 ± 6.4	35.3 ± 5.0	< 0.001
ALT, U/L	23.1 (14.2-39.0)	23.3 (14.0-40.0)	23.0 (16.0-34.0)	0.844	22.0 (13.8-39.0)	21.0 (16.3-33.5)	24.0 (15.9-34.0)	0.801
AST, U/L	28.8 (22.0-40.4)	28.8 (22.0-40.0)	29.0 (20.0-41.0)	0.583	27.0 (21.0-38.0)	26.0 (18.2-36.5)	31.0 (22.0-43.0)[a]	0.034
ALP, U/L	58.0 (46.0-73.0)	58.0 (46.0-73.0)	55.0 (43.5-74.0)	0.171	58.0 (45.0-72.0)	53.0 (38.0-68.5)	58.0 (45.0-77.0)	0.086
TBIL, mmol/L	10.9 (8.2-14.7)	10.8 (8.2-14.5)	11.4 (8.3-15.7)	0.196	10.8 (8.2-14.7)	11.4 (9.5-14.8)	11.3 (8.0-15.8)	0.429
Potassium, mmol/L	3.90 (3.59-4.20)	3.90 (3.60-4.20)	3.88 (3.52-4.21)	0.325	3.94 ± 0.51	3.94 ± 0.49	3.86 ± 0.62	0.279
Sodium, mmol/L	139 (137-141)	140 (137-141)	138 (136-141)	0.001	140 (138-141)[a]	138 (136-141)	139 (136-142)	0.002
Chlorine ion, mmol/L	104 (102-107)	105 (102-107)	103 (100-106)	0.002	104.2 ± 5.3	103.1 ± 4.5	103.7 ± 5.1	0.218
Calcium, mmol/L	2.11 (2.00-2.21)	2.12 (2.01-2.21)	2.09 (1.95-2.17)	0.005	2.13 ± 0.22	2.11 ± 0.22	2.07 ± 0.18	0.011
Phosphorus, mmol/L	1.03 (0.89-1.19)	1.03 (0.89-1.19)	1.01 (0.73-1.18)	0.359	1.04 (0.90-1.19)	1.03 (0.92-1.17)	1.00 (0.85-1.19)	0.300
BUN, mmol/L	3.96 (3.10-5.25)	3.90 (3.10-5.13)	4.68 (3.60-6.20)	< 0.001	3.70 (2.96-4.66)[a]	4.30 (3.51-5.07)	4.93 (3.60-7.01)	< 0.001

Creatinine, μmol/L	63.6 (53.3-78.0)	63.0 (53.0-77.4)	66.3 (54.0-83.8)	0.088	62.00 (52.70-73.00)	60.00 (52.00-76.60)	67.75 (55.25-90.23)[a]	< 0.001
UA, μmol/L	258 (204-336)	257 (205-336)	258 (193-332)	0.725	253 (203-327)	248 (194-306)	264 (191-352)	0.499
CK, U/L	65.0 (43.0-110)	64.5 (44.0-109)	66.5 (40.3-118)	0.830	62.0 (44.0-98.0)	58.5 (36.8-108)	70.0 (43.8-122)	0.233
LDH, U/L	205 (162-272)	201 (160-261)	229 (180-341)	< 0.001	186 (155-239)	198 (164-282)	251 (195-362)[a]	< 0.001
Hs-cTnI > ULN, pg/mL	130 (22.1)	117 (23.4)	13 (14.90)	0.080	71 (23.5)	3 (12.5)	6 (9.5)	0.027
TG, mmol/L	1.22 (0.92-1.78)	1.20 (0.89-1.77)	1.39 (1.04-1.83)	0.002	1.18 (0.86-1.77)	1.50 (1.05-2.08)	1.36 (1.03-1.79)[a]	0.004
TCH, mmol/L	4.00 (3.40-4.80)	4.01 (3.42-4.80)	4.00 (3.22-4.78)	0.180	4.25 ± 1.09	4.34 ± 1.07	3.88 ± 1.08[a]	0.004
LDL-C, mmol/L	2.50 (3.00-3.12)	2.51 (2.02-3.10)	2.48 (1.87-3.15)	0.368	2.65 ± 0.89	2.76 ± 0.91	2.41 ± 0.87[a]	0.020
HDL-C, mmol/L	1.01 (0.82-1.21)	1.03 (0.84-1.24)	0.91 (0.76-1.08)	< 0.001	1.11 ± 0.42[a]	0.97 ± 0.26	0.92 ± 0.27	< 0.001
FPG, mmol/L	5.80 (5.00-7.46)	5.57 (4.92-6.89)	9.10 (6.50-11.63)	< 0.001	5.37 (4.83-6.50)[c]	9.40 (6.48-11.59)	8.80 (6.50-12.03)	< 0.001
3.9-6.9	693 (69.0)	650 (76.7)	43 (27.6)	< 0.001	475 (80.2)[c]	17 (29.8))	26 (26.3)	< 0.001[3]
7.0-11.1	241 (24.0)	179 (21.1)	62 (39.7)		108 (18.2)	22 (38.6)	40 (40.4)	
≥ 11.1	70 (7.0)	19 (2.2)	51 (32.7)		9 (1.5)	18 (31.6)	33 (33.3)	
HbA1C	6.20 (5.55-7.30)	5.90 (5.40-6.30)	7.87 (6.27-9.03)	< 0.001	5.9 (5.44-6.20)[b]	7.60 (5.64-8.98)	7.89 (6.75-9.21)	< 0.001

Data are expressed as *n* (%), mean ± SD or median (IQR). *P* values were calculated by *t* Test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test, One-Way ANOVA or Kruskal-Wallis *H* test as appropriate.

[1]Comparing groups of diabetes and non-diabetes patients.

[2]Comparing groups of non-comorbidity, only diabetes and diabetes with comorbidities.

[3]Mann-Whitney *U* test comparing all subcategories.

Compared with diabetes only group,

[a]$P < 0.05$.

[b]$P < 0.05$.

[c]$P < 0.001$.

ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Urea nitrogen; CK: Creatine kinase; CRP: C reactive protein; FPG: Fasting plasma glucose; Hb: Hemoglobin; HbA1C: Glycosylated hemoglobin; HDL-C: High density lipoprotein cholesterol; Hs-cTnI: Hypersensitive troponin I; LDH: Lactate dehydrogenase; LDL-C: Low density lipoprotein cholesterol; LY: Lymphocyte; NEUT: Neutrophil; NLR: Neutrophil lymphocyte ratio; PCT: Procalcitonin; PLT: Platelet; PT: Prothrombin time; TBIL: Total bilirubin; TCH: Total cholesterol; TG: Triglyceride; UA: Uric acid; WBC: White blood cell.

with non-diabetes patients, more patients with diabetes reported severe cases (34.6% *vs* 21.7%). The diabetes group had a higher rate of ARDS (11% *vs* 5.7%) and hypoproteinemia (15% *vs* 6.5%).

The treatment and primary outcome of the non-comorbidity group and diabetes only group were not different (Table 3), and the results for all-cause mortality were similar in both groups (log-rank $P = 0.59$) (Figure 2B). Regarding the secondary endpoint, there was no difference between the groups except for hypoproteinemia (5.0% *vs* 16.9%). Likewise, there was a similar frequency of COVID-19 pharmacological therapy in the diabetes only patients *vs* diabetes with comorbidities patients; however, the latter was more likely to receive mechanical ventilation (10.8% *vs* 18.3%), had a higher incidence of mortality (4.6% *vs* 18.3%), greater likelihood of shock (0 *vs* 1.6%) and more severe cases (21.5% *vs* 41.3%).

Clinical characteristics and laboratory results of diabetic survivors and non-survivors with COVID-19

Diabetic survivors ($n = 165$) and non-survivors ($n = 26$) shared basic characteristics except for decreased blood oxygen saturation (10.9% *vs* 26.9%) and rapid breathing (18.2% *vs* 26.9%), which were more frequent in non-survivors (Supplementary Table 2), indicating that the latter had severe lung dysfunction. There were numerous

Table 3 Treatments and outcomes of 1331 coronavirus disease 2019 patients divided into different groups

	Tota (*n* = 1331)	Non-diabetes (*n* = 1140)	Diabetes (*n* = 191)	*P*[1] value	Non- comorbidity (*n* = 779)	Diabetes only (*n* = 65)	Diabetes with comorbidities (*n* = 126)	*P*[2] value
Treatments								
Antiviral therapy	1227 (92.2)	1057 (92.7)	170 (89.0)	0.077	725 (93.1)	62 (95.4)	108 (85.7)	**0.010**
Antibiotic therapy	1142 (85.8)	982 (86.1)	160 (83.8)	0.385	665 (85.4)	57 (87.7)	103 (81.7)	0.472
Systemic glucocorticoid	533 (40.0)	458 (40.2)	75 (39.3)	0.813	292 (37.5)	23 (35.4)	52 (41.3)	0.657
Intravenous immunoglobulin	403 (30.3)	342 (30.0)	61 (31.9)	0.590	210 (27.0)	18 (27.7)	43 (34.1)	0.250
Renal replacement therapy	2 (0.2)	1 (0.1)	1 (0.5)	0.267	0 (0.0)	0 (0.0)	1 (0.8)	0.197
Oxygen support								
Oxygenation	786 (59.1)	672 (58.9)	114 (59.7)	0.848	426 (54.7)	38 (58.5)	76 (60.3)	0.446
Mechanical ventilation	154 (11.6)	124 (10.9)	30 (15.7)	0.053	68 (8.7)	7 (10.8)	23 (18.3)	**0.004**
Illness severity								
Severe	313 (23.5)	247 (21.7)	66 (34.6)	**< 0.001**	123 (15.8)	14 (21.5)	52 (41.3)[a]	**< 0.001**
Complications								
ARDS	86 (6.5)	65 (5.7)	21 (11.0)	**0.006**	26 (3.3)	2 (3.1)	19 (15.1)	**< 0.001**
ACI	148 (11.1)	132 (11.6)	16 (8.4)	0.193	77 (9.9)	3 (4.6)	12 (9.5)	0.379
AKI	18 (1.4)	14 (1.2)	4 (2.1)	0.535	6 (0.8)	1 (1.5)	3 (2.4)	0.122
Secondary infection	161 (12.1)	139 (12.2)	22 (11.5)	0.791	76 (9.8)	4 (6.2)	18 (14.3)	0.162
Shock	25 (1.9)	23 (2.0)	2 (1.0)	0.531	9 (1.2)	0 (0.0)	2 (1.6)[a]	0.706
Hypoproteinemia < 30g/l	99 (7.7)	71 (6.5)	28 (15.0)	**< 0.001**	38 (5.0)[c]	11 (16.9)	17 (13.9)	**< 0.001**
Length of hospital stay, d	17.0 (10.0-24.0)	17.0 (10.0-24.0)	16.0 (10.0-25.0)	0.655	17.0 (11.0-24.0)	19.0 (11.5-27.0)	16.0 (8.0-22.5)	0.109
ICU admission	125 (9.4)	103 (9.0)	22 (11.5)	0.276	57 (7.3)	5 (7.7)	17 (13.5)	0.062
Duration from admission to ICU, d	4.00 (1.00-7.50)	5.00 (1.00-8.00)	3.50 (1.75-5.25)	0.383	4.50 (1.00-8.00)	5.00 (1.50-6.00)	3 (1.50-4.50)	0.733
Prognosis								
Death, No	108 (8.1)	82 (7.2)	26 (13.6)	**0.003**	26 (3.3)	3 (4.6)	23 (18.3)	**< 0.001**

Data are expressed as *n* (%), mean ± SD or median (IQR). *P* values were calculated by *t* Test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test, One-Way ANOVA or Kruskal-Wallis *H* test as appropriate.

[1]Comparing groups of diabetic and non-diabetic patients.

[2]Comparing groups of non-comorbidity, only diabetes and diabetes with comorbidities.

Compared with diabetes only group:

[a]$P < 0.05$.

[b]$P < 0.05$.

[c]$P < 0.001$.

ACI: Acute cardiac injury; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome.

differences in laboratory results between diabetic survivors and non-survivors with COVID-19 that reflected the functions of different organs and systems (Supplementary Table 2). Diabetic non-survivors had higher WBC, NEU, NLR, CRP, and IL-6 and lower LY, reflecting that mortality patients had severe inflammatory responses. Serum levels of PT, D-dimer, ALT, AST, BUN, creatinine, CK, and LDH were all significantly higher in non-survivors (Table 4), which reflected more severe coagulation, liver, kidney, and cardiac dysfunction. Diabetic non-survivors reported higher average FPG compared with survivors.

Table 4 Laboratory results of diabetic survivors and non-survivors with coronavirus disease 2019

	Total (*n* = 191)	Survivors (*n* = 165)	Non-survivors (*n* = 26)	*P* value
WBC, × 10^9per L	5.94 (4.49-7.53)	5.91 (4.42-7.29)	7.26(5.19-13.07)	0.016
NEUT, × 10^9per L	4.25 (3.13-5.37)	4.09 (3.01-5.13)	6.22 (3.69-11.33)	< 0.001
LY, × 10^9per L	1.04 (0.72-1.43)	1.08 (0.78-1.48)	0.65 (0.56-1.07)	< 0.001
NLR	3.85 (2.45-6.37)	3.50 (2.33-5.53)	10.43 (5.78-16.84)	< 0.001
Hb, g/L	127.3 ± 16.9	126.8 ± 16.7	131.6 ± 18.3	0.314
PLT, × 10^9per L	196 (147-255)	201 (152-201)	155 (110-230)	0.033
PCT, ng/mL				
< 0.5	143 (94.7)	132 (98.5)	11 (64.7)	< 0.001
≥ 0.5	8 (5.3)	2 (1.5)	6 (35.3)	
CRP	29.8 (5.5-75.9)	25.4 (4.4-63.0)	115.3 (66.1-170.6)	< 0.001
IL-6, pg/mL	3.31 (1.64-17.49)	3.09 (1.50-5.25)	83.47 (35.75-243.60)	< 0.001
PT, s	14.30 (11.90-15.50)	14.00 (11.60-15.40)	16.20 (13.52-18.92)	0.002
< 16	116 (76.8)	110 (81.5)	6 (37.5)	< 0.001
≥ 16	35 (23.2)	25 (18.5)	10 (62.5)	
D-dimer, mg/L	0.69 (0.35-1.35)	0.62 (0.62-1.09)	5.40 (1.50-21.00)	< 0.001
≤ 0.5	58 (37.9)	57 (41.9)	1 (5.9)	< 0.001
> 0.5 to ≤ 1.0	46 (30.1)	43 (31.6)	3 (17.6)	
> 1.0	49 (32.0)	36 (26.5)	13 (76.5)	
ALB, g/L	35.7 ± 5.5	36.0 ± 30.5	33.5 ± 23.4	0.031
ALT, U/L	23.0 (16.0-34.0)	21.3 (15.3-32.3)	31.0 (20.9-46.6)	0.008
AST, U/L	29.0 (20.0-41.0)	27.0 (19.0-38.7)	43.0 (31.0-60.5)	< 0.001
ALP, U/L	55.0 (43.5-74.0)	55.0 (41.5-73.0)	57.0 (49.5-89.5)	0.241
TBIL, mmol/L	11.3 (8.3-15.7)	11.4 (9.0-15.1)	11.2 (7.6-28.0)	0.642
Potassium, mmol/L	3.88 (3.52-4.21)	3.90 (3.54-4.21)	3.65 (3.37-4.30)	0.381
Sodium, mmol/L	138.4 ± 4.3	138.2 ± 3.9	139.3 ± 6.4	0.418
Chlorine ion, mmol/L	103.5 ± 4.9	103.2 ± 4.7	105.3 ± 6.0	0.052
Calcium, mmol/L	2.09 (1.95-2.17)	2.10 (1.95-2.20)	2.00 (1.89-2.11)	0.042
Phosphorus, mmol/L	1.01 (0.86-1.18)	1.02 (0.87-1.19)	0.93 (0.76-1.18)	0.268
BUN, mmol/L	4.70 (3.60-6.22)	4.5 (3.59-5.82)	6.51 (4.92-17.45)	< 0.001
Creatinine, μmol/L	66.3 (54.0-83.8)	64.0 (44.6-81.0)	73.0 (64.0-129.6)	0.006
UA, μmol/L	258 (193-332)	258 (147-321)	293 (179-428)	0.286
CK, U/L	66.5 (40.3-117.8)	61.0 (36.5-111.0)	85.0 (71.0-364.0)	0.002
LDH, U/L	229 (180-341)	216 (172-219)	522 (420-611)	< 0.001
Hs-cTnI > ULN, pg/mL	10/88 (11.4)	8/72 (11.1)	2/16 (12.5)	1.000
TG, mmol/L	1.39 (1.04-1.83)	1.41 (1.05-1.98)	1.31 (0.99-1.57)	0.398
TCH, mmol/L	4.04 ± 1.10	4.12 ± 1.06	3.39 ± 1.16	0.009
LDL-C, mmol/L	2.54 ± 0.90	2.59 ± 0.88	2.10 ± 0.93	0.036
HDL-C, mmol/L	0.94 ± 0.26	0.94 ± 0.26	0.89 ± 0.33	0.450
FPG, mmol/L	9.10 (6.50-11.72)	8.70 (6.50-11.36)	12.00 (9.40-16.81)	0.011
3.9-6.9	43 (27.7)	40 (28.6)	3 (20.0)	0.069[1]
7.0-11.1	61 (39.4)	58 (41.4)	3 (20.0)	

≥ 11.1	51 (32.9)	42 (30.0)	9 (60.0)	
HbA1C	7.77 ± 1.97	7.61 ± 1.90	9.53 ± 2.02	0.021

Data are expressed as *n* (%), mean ± SD or median (IQR). *P* values were calculated by *t* Test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test as appropriate. [1]Mann-Whitney *U* test comparing all subcategories.

P: Comparing groups of diabetic survivors and non-survivors; ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Urea nitrogen; CK: Creatine kinase; CRP: C reactive protein; FPG: Fasting plasma glucose; Hb: Hemoglobin; HbA1C: Glycosylated hemoglobin; HDL-C: High density lipoprotein cholesterol; Hs-cTnI: Hypersensitive troponin I; LDH: Lactate dehydrogenase; LDL-C: Low density lipoprotein cholesterol; LY: Lymphocyte; NEUT: Neutrophil; NLR: Neutrophil lymphocyte ratio; PCT: Procalcitonin; PLT: Platelet; PT: Prothrombin time; TBIL: Total bilirubin; TCH: Total cholesterol; TG: Triglyceride; UA: Uric acid; WBC: White blood cell.

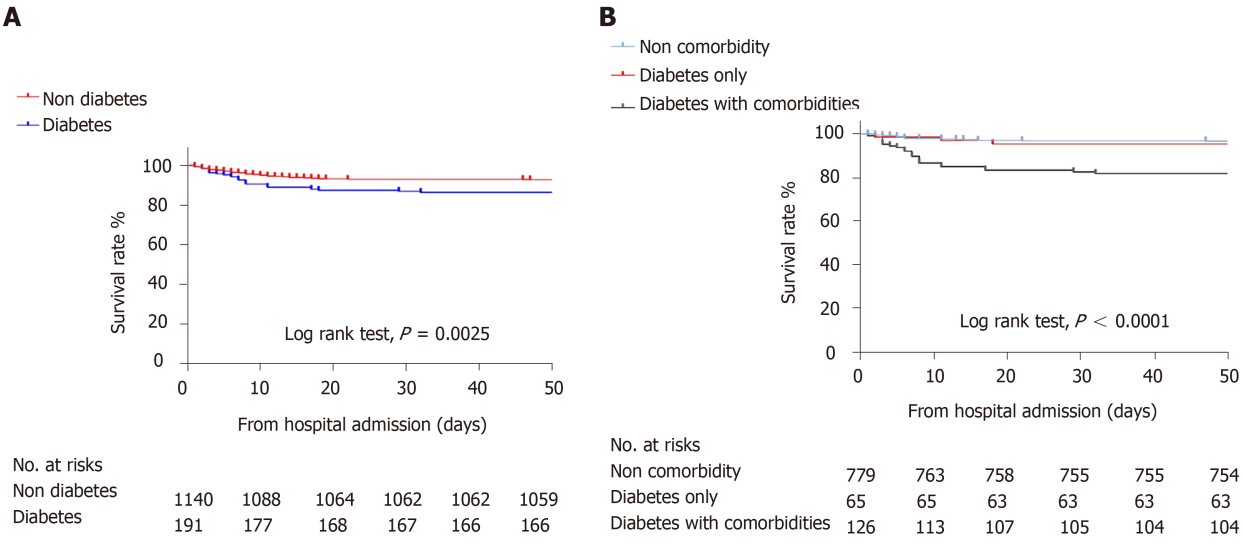

Figure 2 Kaplan-Meier survival curves of in-hospital mortality among patients with coronavirus disease 2019. A: Kaplan-Meier survival curves for in-hospital mortality between diabetes and non-diabetes patients from hospital admission. B: Kaplan-Meier survival curves for in-hospital mortality comparison of patients without comorbidities, diabetes only and diabetes with comorbidities from hospital admission. Patients without comorbidities and diabetes were compared only from hospital admission (log rank test, *P* = 0.590). Patients with only diabetes and diabetes with comorbidities from hospital admission were compared (log rank test, *P* = 0.009).

Treatment and outcome of diabetic survivors and non-survivors with COVID-19

Undoubtedly, higher proportions of complications, including ARDS (3.0 *vs* 61.5%), ACI (5.5% *vs* 26.9%), shock (0 *vs* 11.5%), secondary infection (6.1% *vs* 46.2%), AKI (0.6% *vs* 7.7%) and coagulopathy (15.8% *vs* 38.5%), were found in non-survivors (Table 5). Likewise, the non-survivor group had a greater incidence of severe cases (33.7% *vs* 100%) and ICU admission (6.7% *vs* 42.3%) and was more likely to receive corticosteroids (33.3% *vs* 73.1%). There was a significantly lower frequency of hypoglycemic medication in diabetic non-survivors *vs* diabetic survivors, including metformin (30.9% *vs* 11.5%), sulfonylurea (21.8% *vs* 3.8%) and acarbose (45.5% *vs* 7.7%), which might be related to controlled blood glucose.

Clinical characteristics, laboratory results, treatment and outcome of patients with diabetes with COVID-19 using metformin and matched non-metformin users

Of 191 patients with diabetes with COVID-19, 54 cases were using metformin, and after sex and age matching, there were 50 patients using metformin and 50 sex- and age-matched non-metformin users. The frequency of fever (54% *vs* 78%) and fatigue (38% *vs* 18%) showed significant differences in clinical characteristics between patients with diabetes with COVID-19 using metformin and matched non-metformin users (Supplementary Table 3). Laboratory findings (Table 6) revealed that metformin users had lower levels of LDH and FPG; however, the distribution of glucose was similar. The results that referred to liver, kidney, cardiac, coagulation and inflammatory response function were not statistically significant. The primary outcome and secondary outcome of patients who used metformin were comparable to matched non-metformin users (Table 7). The former group showed a higher need for antivirals (98% *vs* 84%) and antibiotics (90% *vs* 74%). Insulin (52.0% *vs* 20%), sulfonylurea (36.0% *vs*

Table 5 Treatments and outcomes of diabetic survivors and non-survivors with coronavirus disease 2019

	Total (*n* = 191)	Survivors (*n* = 165)	Non-survivors (*n* = 26)	*P* value
Treatments				
Antiviral therapy	170 (89.0)	149 (90.3)	21 (80.8)	0.268
Antibiotic therapy	160 (83.8)	139 (84.2)	21 (80.8)	0.873
Systemic glucocorticoids	74 (38.7)	55 (33.3)	19 (73.1)	**< 0.001**
Intravenous immunoglobulin	60 (31.4)	50 (30.3)	10 (38.5)	0.405
Renal replacement therapy	1 (0.5)	0 (0.0)	1 (3.8)	0.136
Insulin	88 (46.1)	75 (45.5)	13 (50.0)	0.666
Metformin	54 (28.3)	51 (30.9)	3 (11.5)	**0.041**
Sulfonylurea	37 (19.4)	36 (21.8)	1 (3.8)	**0.031**
DPP-4 inhibitor	11 (5.8)	10 (6.1)	1 (3.8)	1.000
Acarbose	77 (40.3)	75 (45.5)	2 (7.7)	**< 0.001**
Thiazolidinedione	7 (3.7)	7 (4.2)	0 (0.0)	0.596
Oxygen support				
Oxygenation	115 (60.2)	95 (57.6)	20 (76.9)	0.061
Mechanical ventilation	35 (18.3)	15 (9.1)	20 (76.9)	**< 0.001**
Illness severity				
Severe	63 (33.0)	37 (33.7)	26 (100)	**< 0.001**
Complications				
ARDS	21 (11.0)	5 (3.0)	16 (61.5)	**< 0.001**
ACI	16 (8.4)	9 (5.5)	7 (26.9)	**0.001**
AKI	3 (1.6)	1 (0.6)	2 (7.7)	**0.049**
Secondary infection	22 (11.5)	10 (6.1)	12 (46.2)	**< 0.001**
Shock	3 (1.6)	0 (0.0)	3 (11.5)	**0.002**
Hypoproteinemia < 30 g/L	28 (14.7)	22 (13.3)	6 (23.1)	0.314
Coagulopathy	36 (18.8)	26 (15.8)	10 (38.5)	**0.013**
Length of hospital stay, d	16.0 (10.0-25.0)	18.0 (11.5-26.0)	7.0 (3.0-11.0)	**< 0.001**
ICU admission	22 (11.5)	11 (6.7)	11 (42.3)	**< 0.001**
Duration from admission to ICU, d	4.00 ± 3.51	3.91 ± 3.11	4.09 ± 4.01	0.907

Data are expressed as *n* (%), mean ± SD or median (IQR). *P* values were calculated by *t* Test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test as appropriate. Comparing groups of diabetic survivors and non-survivors. ACI: Acute cardiac injury; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome.

2%), acarbose (56.0% *vs* 6%), and thiazolidinedione (12% *vs* 0) were also applied significantly more frequently to the individuals using metformin.

Clinical characteristics, laboratory results, treatment and outcome of patients with diabetes with COVID-19 using acarbose and matched non-acarbose users

Of 191 patients with diabetes with COVID-19, 77 cases were treated with acarbose, and after sex and age matching, there were 46 patients treated with acarbose and 46 sex- and age-matched non-acarbose users. Supplementary Table 3 shows that the length of symptom onset to hospital admission was longer in the acarbose group than in the matched non-acarbose group, which indicated that the symptoms in the former patients might be relatively mild. Notably, some inflammatory response-related laboratory results, such as WBC, NLR, and CRP, were significantly lower in the acarbose group (Table 6). Furthermore, these differences were not related to glucose control, as the serum level of glucose in both groups was comparable.

Table 6 Laboratory results of diabetic coronavirus disease 2019 patients using metformin or acarbose and matched non-metformin or non-acarbose inhibitor user

	Metformin (*n* = 50)	Matched non-Metformin (*n* = 50)	Acarbose (*n* = 46)	Matched non-acarbose (*n* = 46)
WBC, × 10^9/L	6.33 ± 2.25	6.27 ± 2.62	4.83 (4.04-6.68)	5.91 (4.42-9.35)[c]
NEUT, × 10^9/L	4.20 (3.02-5.18)	4.17 (3.21-5.87)	3.50 (2.48-4.74)	4.60 (3.14-8.13)
LY, × 10^9/L	1.20 (0.69-1.74)	1.14 (0.82-1.50)	1.19 ± 0.55	1.04 ± 0.53
NLR	3.69 (2.11-6.05)	3.74 (2.47-5.55)	3.25 (2.05-4.41)	4.88 (2.50-12.32)[d]
Hb, g/L	126.0 ± 15.7	126.5 ± 14.9	126.0 ± 16.9	129.3 ± 17.3
PLT, × 10^9/L	229.5 ± 93.5	208.5 ± 103.8	233.0 ± 93.2	214.2 ± 99.7
PCT, ng/mL				
< 0.5	43 (100.0)	34 (91.9)	37 (100.0)	34 (87.2)
≥ 0.5	0 (0.0)	3 (8.1)	0 (0.0)	5 (12.8)
CRP	50.7 (5.0-78.0)	46.5 (6.3-106.8)	26.2 (3.7-52.2)	63.8 (10.8-83.4)[c]
IL-6, pg/mL	2.07 (1.50-4.90)	3.20 (1.68-67.28)	2.58 (1.50-5.06)	19.88 (1.95-67.28)
PT, s	13.5 ± 2.7	14.2 ± 2.2	14.1 ± 2.6	14.2 ± 3.2
< 16	37 (86.0)	31 (79.5)	30 (78.9)	27 (73.0)
≥ 16	6 (14.0)	8 (20.5)	8 (21.1)	10 (27.0)
D-dimer, mg/L	0.45 (0.26-1.19)	0.83 (0.33-1.60)	0.59 (0.33-0.98)	0.96 (0.39-5.40)
≤ 0.5	22 (52.4)	13 (33.3)	18 (42.9)	12 (33.3)
> 0.5 to ≤ 1.0	6 (14.3)	11 (28.2)	15 (35.7)	7 (19.4)
> 1.0	14 (33.3)	15 (38.5)	9 (21.4)	17 (47.2)
ALB, g/L	35.7 ± 5.9	35.8 ± 5.5	35.7 ± 6.5	35.1 ± 4.8
ALT, U/L	20.0 (13.5-27.5)	22.0 (17.0-36.0)	20.0 (14.0-31.0)	23.00 (14.00-33.25)
AST, U/L	25.5 (18.5-33.7)	29.0 (20.0-42.0)	23.0 (17.5-36.4)	31.0 (21.5-39.6)
ALP, U/L	51.0 (37.0-71.0)	54.0 (44.0-68.0)	59.5 24.6	61.5 25.5
TBIL, mmol/L	12.2 ± 5.4	13.4 ± 16.2	11.5 ± 4.8	13.5 ± 5.4
Potassium, mmol/L	3.81 ± 0.46	3.77 ± 0.54	3.90 ± 0.50	3.82 ± 0.63
Sodium, mmol/L	137.9 ± 3.9	138.2 ± 4.1	138. 5 ± 3.8	138.1 ± 4.7
Chlorine ion, mmol/L	103.3 ± 4.5	103.4 ± 5.0	103.2 ± 4.6	103.7 ± 5.3
Calcium, mmol/L	2.14 ± 0.22	2.05 ± 0.18[a]	2.12 ± 0.22	2.08 ± 0.19
Phosphorus, mmol/L	1.02 (0.83-1.21)	0.99 (0.87-1.17)	1.07(0.88-1.21)	1.00 (0.77-1.21)
BUN□mmol/L	4.40 (3.67-4.84)	5.20 (3.50-5.75)	4.16 (3.60-5.18)	5.04 (3.80-6.64)
Creatinine, μmol/L	54.0 (49.0-73.7)	60.0 (52.5-90.3)	59.5 (48.8-74.5)	68.0 (55.0-89.3)
UA, μmol/L	266.5 ± 96.6	260.9 ± 98.7	229 (168-263)	258 (179-324)
CK, U/L	64.0 (49.0-84. 0)	82.0 (39.0-135.3)	53.5 (35.5-73.8)	71.0 (40.0-114.0)
LDH, U/L	237 ± 115	304 ± 162[a]	229 (185-263)	267 (181-446)
Hs-cTnI > ULN , pg/mL	0/24 (0.0)	3/15 (20.0)	1/21 (4.8)	2/26 (7.7)
TG, mmol/L	1.55 (1.15-1.82)	1.32 (1.08-3.40)	1.36 (1.05-1.83)	1.15 (0.94-1.61)
TCH, mmol/L	3.91 ± 0.87	3.80 ± 0.92	4.40 ± 1.14	4.04 ± 0.96
LDL-C, mmol/L	2.40 ± 0.73	2.43 ± 0.78	2.84 ± 0.87	2.57 ± 0.83
HDL-C, mmol/L	0.93 ± 0.22	0.88 ± 0.28	0.98 ± 0.27	0.93 ± 0.23
FPG, mmol/L	10.57 ± 4.92	8.32 ± 2.47[b]	9.92 ± 4.90	10.00 ± 4.26

3.9-6.9	11 (44.0)	13 (38.2)	12 (30.8)	8 (22.2)
7.0-11.1	13 (52.0)	21 (61.8)	13 (33.3)	16 (44.4)
≥ 11.1	1 (4.0)	0 (0.0)	14 (35.9)	12 (33.3)
HbA1C	7.96 ± 1.85	6.71 ± 1.94	7.85 ± 1.78	8.25 ± 2.04

Data are expressed as *n* (%), mean ± SD or median (IQR). *P* values were calculated by *t* Test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test as appropriate.
Comparison of metformin users and non-users:
[a]$P < 0.05$.
[b]$P < 0.01$.
Comparison of acarbose users and non-users:
[c]$P < 0.05$.
[d]$P < 0.01$.
ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Urea nitrogen; CK: Creatine kinase; CRP: C reactive protein; FPG: Fasting plasma glucose; Hb: Hemoglobin; HbA1C: Glycosylated hemoglobin; HDL-C: High density lipoprotein cholesterol; Hs-cTnI: Hypersensitive troponin I; LDH: Lactate dehydrogenase; LDL-C: Low density lipoprotein cholesterol; LY: Lymphocyte; NEUT: Neutrophil; NLR: Neutrophil lymphocyte ratio; PCT: Procalcitonin; PLT: Platelet; PT: Prothrombin time; TBIL: Total bilirubin; TCH: Total cholesterol; TG: Triglyceride; UA: Uric acid; WBC: White blood cell.

The mortality rate (2.2% *vs* 26.1%) was lower in the acarbose group (Table 7), as were the rates of ARDS (2.2% *vs* 17.4%) and shock (2.2% *vs* 21.7%). At the same time, patients who were treated with acarbose indicated a lower need for treatment with corticosteroids (26.1% *vs* 47.8%), immunoglobin (23.9% *vs* 47.8%), mechanical ventilation (6.5% *vs* 21.7%), and insulin (50.0% *vs* 84.8%).

Independent risk factors for mortality of patients with COVID-19

Among the 1131 included patients, multivariable Cox regression (Table 8) showed that male [hazard ratio (HR) 2.59, 95%CI 1.63-3.99], hypertension (HR 1.75, 95%CI 1.18-2.6), CKD (HR 4.55, 95%CI 2.52-8.20), and CVD (HR 2.35, 95%CI 1.27-4.33) were risk factors for COVID-19 mortality. Age was also a risk factor for COVID-19 mortality. However, diabetes alone was not an independent risk factor for mortality in patients with COVID-19.

DISCUSSION

A number of studies have demonstrated that patients with diabetes have a higher risk of mortality from COVID, as well as a greater risk of developing more severe cases[4,7,12,13]. Guo *et al*[13] reported that diabetes was a risk factor for the progression and prognosis of COVID-19. However, Shi *et al*[14] pointed out that diabetes was not independently associated with COVID mortality, while commonalities, such as hypertension and cardiovascular disease, played more important roles in contributing to the in-hospital death of patients with COVID-19, which was relatively limited in size. In this study, which had relatively rich clinical data, we found that diabetes alone was not an independent risk factor for in-hospital mortality from COVID-19, but comorbidities such as hypertension and CKD were risk factors; this result was consistent with a previous study[14]. Partially consistent with previous studies, our study found that compared with non-diabetic patients, patients with diabetes with COVID-19 were older, had worse outcomes, including a higher rate of mortality, severe cases and ARDS, and presented severe inflammatory response, lung and coagulation dysfunction[7,13,15]. In this study, up to 88% of diabetic patients were greater than or equal to 50 years of age, more over, older age was an independent risk factor of mortality in COVID-19, which was consistent with previous studies[3,14]. Additionally, patients with diabetes had increased levels of urea nitrogen and decreased levels of albumin. These abnormalities indicated that COVID-19 may be associated with progressive organ injury in patients with diabetes. Preexisting hypertension, CHD, CVD, and CKD had higher frequencies in the diabetic group. Recent studies reported that patients with cardiovascular hypertension, CKD, and CVD were more likely to develop severe cases[4,6,16], so we compared patients with diabetes and COVID-19 without comorbidity and patients with COVID-19 without any comorbidity to identify whether diabetes without comorbidity was a risk factor for COVID-19. In our study, there was no difference in the outcome between the non-comorbidity group and the diabetes only group. Shi *et al*[16] reported that even though

Table 7 Treatments and outcomes of diabetic coronavirus disease 2019 patients using metformin and matched non-metformin, acarbose and matched non-acarbose

	Metformin (*n* = 50)	Matched non-Metformin (*n* = 50)	Acarbose (*n* = 46)	Matched non-acarbose (*n* = 46)
Treatments				
Antiviral therapy	49 (98.0)	42 (84.0)[a]	41 (89.1)	43 (93.5)
Antibiotic therapy	45 (90.0)	37 (74.0)[a]	40 (87.0)	40 (87.0)
systemic glucocorticoids	17 (34.0)	16 (32.0)	12 (26.1)	22 (47.8)[e]
Intravenous immunoglobulin	15 (30.0)	11 (22.0)	11 (23.9)	22 (47.8)[e]
Renal replacement therapy	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Insulin	26 (52.0)	10 (20.0)[b]	23 (50.0)	39 (84.8)[g]
Metformin	50	0	21 (45.7)	15 (32.6)
Sulfonylurea	18 (36.0)	1 (2.0)[c]	17 (37.0)	8 (17.4)[e]
DPP-4 inhibitor	3 (6.0)	0 (0.0)	3 (6.5)	3 (6.5)
Acarbose	28 (56.0)	3 (6.0)[c]	46 (100.0)	0 (0.0)
thiazolidinedione	6 (12.0)	0 (0.0)[a]	4 (8.7)	0 (0.0)
Oxygen support				
Oxygenation	32 (64.0)	21 (42.0)	30 (65.2)	30 (65.2)
Mechanical ventilation	6 (12.0)	11 (22.0)	3 (6.5)	10 (21.7)[e]
Illness severity				
Severe	14 (28.0)	21 (42.0)	12 (26.1)	18 (39.1)
Complications				
ARDS	4 (8.0)	8 (16.0)	1 (2.2)	8 (17.4)[e]
ACI	1 (2.0)	4 (8.0)	2 (4.3)	6 (13.0)
AKI	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)
Secondary infection	8 (16.0)	5 (10.0)	0 (0.0)	2 (4.3)
Shock	1 (2.0)	0 (0.0)	1 (2.2)	10 (21.7)[e]
Hypoproteinemia < 30 g/L	9 (18.0)	5 (10.0)	10 (21.7)	6 (13.0)
Coagulopathy	6 (12.0)	9 (18.0)	8 (17.4)	10 (21.7)
Length of hospital stay, d	17.60 ± 8.74	16.80 ± 10.51	18.37 ± 8.15	16.52 ± 9.96
ICU admission	6 (12.0)	6 (12.0)	3 (6.5)	8 (17.4)
Duration from admission to ICU, d	3.83 ± 2.04	2.83 ± 2.14	6.00 (3.50-6.00)	2.50 (2.00-5.00)
Prognosis				
Discharged	47 (94)	41 (82)	45 (97.8)	34 (73.9)[f]
Death	3 (6.0)	9 (18)	1 (2.2)	12 (26.1)

Data are expressed as *n* (%), mean ± SD or median (IQR). *P* values were calculated by *t* Test, Mann-Whitney *U* test, χ^2 test, Fisher's exact test as appropriate.
Comparison of metformin users and non-users:
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Comparison of acarbose users and non-users:
[e]$P < 0.05$.
[f]$P < 0.01$.
[g]$P < 0.001$.
ACI: Acute cardiac injury; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome.

patients with COVID-19 with diabetes had worse outcomes, it was not independently

Table 8 Multivariate COX regression analysis on the risk factors associated with mortality of 1331 coronavirus disease 2019 patients

Factor	Hazard ratio	*P* value
Sex (male)	2.59 (1.68-3.99)	< 0.001
Age, yr		
18-49	1 (ref)	
50-64	5.86 (2.27-15.12)	< 0.001
≥ 65	11.8 (4.6- 30.2)	< 0.001
Hypertension	1.75 (1.18-2.60)	0.006
CKD	4.55 (2.52-8.20)	< 0.001
CVD	2.35 (1.27-4.33)	0.006
Diabetes	0.98 (0.62-1.54)	0.918

CKD: Chronic kidney disease; CVD: Cerebrovascular disease.

associated with in-hospital death, which was consistent with our results. In addition, most laboratory results were comparable between the non-comorbidity group and the diabetes only group, except for CRP, albumin, sodium, urea nitrogen, HDL-C and, of course, blood glucose. CRP is an inflammatory biomarker that is related to glucose homoeostasis, obesity and atherosclerosis[17] and was independently related to insulin sensitivity[18]. In addition, insulin resistance was a main characteristic of type 2 diabetes; since CRP was related to the chronic inflammatory situation, and the levels of WBC, NEU, and LY, which reflected the acute infection with the disease pathogen, were not statistically significant, we inferred that diabetes itself did not increase the degree of inflammation after SARS-CoV-2 infection.

Patients with diabetes with comorbidities were more seriously ill when compared with the diabetes only group and non-comorbidity group. The mortality was higher in the diabetes with comorbidities group, but the difference between both diabetes groups had no relation to FPG because the median FPG in both diabetes groups was comparable. Patients with diabetes with comorbidity were 10 years older than patients who had no comorbidity except diabetes; furthermore, age ≥ 65 years was associated with a greater risk of death[4]. As described above, patients with hypertension and CVD were more likely to develop severe cases[4]. Furthermore, our analysis indicated that age, hypertension, CKD, and CVD were risk factors for COVID-19 mortality. Since the diabetes with comorbidities group had a higher prevalence of hypertension, CKD and CVD, there was no doubt that patients with diabetes with comorbidities had worse outcomes.

Comparing to the survivor of diabetic patients with COVID-19, the diabetic patients who died of COVID-19 had more severe inflammatory response, progressive organ injury, and also, undoubtedly, higher proportions of complications and severe cases. Randomised Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group[19] and WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group[20] reported that systemic glucocorticoids was conducive to the reduction in mortality of COVID-19 severe cases. As the percentage of severe case in non-survivor group were 100%, while that rate in survivor group was just 33%, there was no doubt that non-survivor group had higher rate of using systemic glucocorticoids. Therefore, in such cases, higher rate of systemic glucocorticoids treatment in non-survivor group did not indicated higher rate of mortality in systemic glucocorticoids treatment.

One unanticipated result was that acarbose, not metformin, could improve prognosis through a decrease in the degree of inflammation, which was independent of the blood glucose level. In addition, acarbose accounted for 97% of the glycosidase inhibitors used. Feng *et al*[21] reported that acarbose could effectively block the metastasis of enterovirus 71 (EV71) from the intestine to the whole body. EV71 is one of the main causes of hand-foot-and-mouth disease (HFMD), and its infection relies on the interaction of the canyon region of its virion surface and the glycosylation of the SCARB2 protein, which is the cellular receptor of EV71 infection. Dang *et al*[22] found that acarbose not only inhibited cellular receptors of various glycosylated viruses but also competitively blocked the canyon region of the EV71 virion surface, blocking the metastasis of EV71 from the intestine. Angiotensin converting enzyme II (ACE2) is a SARS-CoV-2 cell entry receptor[23], and glycosylation sites play an important role in

the combination of SARS-CoV-2 and its receptor[24,25]. Chloroquine was reported to block SARS-CoV-2 infection by interfering with the glycosylation of cellular receptors [26]. As previously stated, acarbose inhibited the glycosylation of EV71 receptors; additionally, patients with diabetes with COVID-19 who were treated with acarbose had better outcomes than patients who were not treated, suggesting that acarbose could improve the prognosis of COVID-19 infection by inhibiting the glycosylation of ACE2. In addition, compared to the non-acarbose group, the acarbose group had lower WBC, NLR, and CRP levels, indicating a decreased inflammatory response and further supporting the anti-SARS-CoV-2 function of acarbose. Furthermore, a previous study showed that acarbose could change the gut microbiota and then beneficially regulate the body's immune function[27]. A recent study revealed that fetal microbiome changes occurred in patients with COVID-19, characterized by depletion of beneficial commensals and enrichment of opportunistic pathogens[28]. Therefore, we inferred that acarbose might increase the baseline abundance of microbiota that had inversely correlated with COVID-19.

As previous studies reported that metformin has multiple additional health benefits in patients with diabetes[29], we anticipated that metformin would improve prognosis after COVID-19 infection; however, the results were unexpected. Scanning the literature, we found that metformin improves ACE2 stability through AMPK[30], which means that metformin may increase ACE2 availability. In addition, the median level of FPG was higher in metformin users than in nonusers, as a previous study reported that improving glycemic control substantially reduced the risk of mortality from COVID-19.

The study has some limitations. First, due to the retrospective and multiple-center study design, some information, such as patients' exposure history, the chronic disease severity and medication, diabetes medication, glycemic control and several laboratory items, was not available for all patients. There could be assay variability in different centers. Second, samples were only from Hubei Province, China; thus, more studies in other regions, even other countries, might obtain more comprehensive insight into COVID-19. However, this study is one of the largest retrospective and multicenter studies among patients with COVID-19. Additionally, this study is one of the first to investigate the influence of diabetes medications in patients with diabetes with COVID-19. The relatively abundant clinical data and numerous events also strengthen the results. The conclusion will help clinicians identify high-risk patients and choose suitable diabetes medication for patients with diabetes.

CONCLUSION

In conclusion, patients with diabetes had worse outcomes when suffering from COVID-19; however, the outcome was not related to diabetes itself but to comorbidities such as hypertension, CKD and CVD. Furthermore, the administration of acarbose could reduce the risk of death, ARDS, and shock in patients with diabetes.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) has become an ongoing pandemic and has caused considerable mortality worldwide. Previous studies have demonstrated that patients with diabetes have a higher risk of mortality from COVID-19, as well as a greater risk of developing more severe cases.

Research motivation

Diabetes was a risk factor for the progression and prognosis of COVID-19, however, the effects of diabetes or anti-diabetic medication on the mortality of COVID-19 have not been well described.

Research objectives

We aim to investigate the outcome of different statuses (with or without comorbidity) and anti-diabetic medication use before admission of diabetic after COVID-19.

Research methods

The clinical characteristics of 1422 consecutive hospitalized patients were collected. The statistical analyses were conducted with SPSS (version 25.0).

Research results

The overall survival rate was significantly lower in the diabetes group (log-rank $P < 0.01$), but the results for all-cause mortality were similar in the non-comorbidity group and diabetes only group (log-rank $P = 0.59$). Male sex [hazard ratio (HR) 2.59, $P < 0.001$], hypertension (HR 1.75, $P = 0.006$), chronic kidney disease (CKD) (HR 4.55, $P < 0.001$), cerebrovascular disease (CVD) (HR 2.35, $P = 0.006$), and age were independent risk factors for the COVID-19 mortality in multivariable Cox regression. However, diabetes alone was not an independent risk factor for mortality in patients with COVID-19.

Research conclusions

Although diabetes is associated with a higher risk of mortality in patients with COVID-19, the outcome was not related to diabetes itself. Age, hypertension, CKD and CVD were the independent risk factor of mortality.

Research perspectives

The present study calls more attention to the impact of older age and comorbid chronic disease, such as hypertension, CKD and CVD on disease progression among diabetic patients with COVID-19.

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