Diabetic Patients with Comorbidities had Worse Outcomes When Suffered with COVID-19 and Acarbose might have Protective Effects

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Abstract

Background: Previous studies showed that diabetes was a common comorbidity of COVID-19, but the effects of diabetes or anti-diabetic drugs on the mortality of COVID-19 have not been well described. To investigate the outcome of different status (with or without comorbidity) and anti-diabetic medication before admission of diabetic patients after SARS-CoV-2 infected, we collected clinical data of COVID-19 patients from Hubei Province and compared between diabetes and non-diabetes.

Methods: In this multicenter and retrospective study, we enrolled 1,422 cases of 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.

Results: Diabetes patients were 10-years older than non-diabetes (p<0.001), had higher prevalence of comorbidities such as hypertension (p<0.001), coronary heart disease (p<0.001), cerebrovascular disease (CVD) (p<0.001), chronic kidney disease (CKD) (p=0.007). The incidence of mortality (p=0.003) were more prevalent among the diabetes group. Further analysis revealed that diabetes patients who took alpha-glucosidase inhibitor (AGI) had lower mortality rate(p<0.01). Multivariable Cox regression showed that male sex, hypertension, CKD, CVD, age were risk factors for the mortality of COVID-19. Survival curve revealed that, compared with diabetes only group, the mortality was increased in diabetes with comorbidities (p=0.009), but had no significant difference in the non-comorbidity group, p=0.59).

Conclusions: Patients with diabetes had worse outcome when suffered with COVID-19, however, it was not associated with diabetes itself but the comorbidities. Furthermore, the administration of AGI could reduce the risk of death in patients with diabetes.

Introduction

Corona Virus Disease 2019 (COVID-19) had become an ongoing pandemic and caused considerable mortality all over the world[1]. Diabetes is a common comorbidity especially in elderly patients, but the effects of diabetes or anti-diabetic drugs on the severity and mortality of COVID-19 have not been well described. Severe cases of COVID-19 can rapidly progress to critical situation, and COVID-19 has been declared as a public health emergency by the World Health Organization (WHO), however there is no specific medicine to cure it until now. As of Jun 27, 2020, more than nine million COVID-19 cases have been confirmed around the world, and nearly 480,000 patients died of COVID-19 (http://www.who.int/emergencies /diseases/novel -coronavirus-2019 situation -reports). Well-controlled blood glucose of pre-existing diabetes was associated with a significant reduction in the composite adverse outcomes and death of COVID-19 patients [2]. As we all known, patients with diabetes often had several comorbidities, and previous research had revealed that hypertension, chronic obstructed pneumonia disease (COPD),chronic kidney disease (CKD), cardiovascular disease and cerebrovascular disease (CVD) were also associated with worse outcome in patients suffered with COVID-19 [3-6]. However, fewer studies described the outcome of different comorbidity status of diabetic patients after infected COVID-19. Besides, fewer studies focus on whether anti-diabetic medication would influence the outcome of pre-existing diabetes patients who suffer with COVID-19. In this study, we perform multicenter study to investigate the outcome of different status (with or without comorbidity) and anti-diabetic medication before admission of diabetic patients after SARS-CoV-2 infected.

Material And Method

Study design and participants

This is multicenter, observational, retrospective and real world study which included six designated tertiary centers (**Tabel S1**) of adult inpatients between January 21,2020 and March25, 2020. A total of 1422 patients with COVID-19 were screened for this study. All patients were diagnosed with COVID-19 in accordance with WHO interim guidance. **Figure 1** shows the patients selection flow for this study.

Data collection

Epidemiological material, demographic, clinical, laboratory parameters, radiographic characteristics, treatment and outcome were extracted from electronic medical records using a standardized data collection form. Major clinical symptoms, vital signs at admission and comorbidities were collected. The treatment data was not just included COVID-19 but also diabetes mellitus.

Duration from onset symptoms to admission, illness severity, 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 drugs, otherwise, newly diagnosed diabetes was based on the serum level of fasting blood glucose (FBG) (≥7.0mmol/L), random blood glucose (≥11.1mmol/L), glycosylated hemoglobin (HbA1c) ≥6.5% and classic symptoms of hyperglycemia during hospital stay (As oral glucose tolerance test may lead to hyperglycemia, then worsening of COVID-19 patient's illness, it was not used for diagnosis of diabetes in our study). Hypertension was defined by a history hypertension, or use of anti-hypertensive drugs, or according to the National Heart Lung and Blood Institute criteria [7]. 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 [8]. Acute kidney injury (AKI) was diagnosed according to the KDIGO clinical practice guideline [9]. 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 was according to the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) [10]. 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, incidence of SARS-CoV-2-related complications including ARDS, AKI, ACI, secondary infection, shock and hypoproteinemiae.

Data analyses

Continuous variables were described as median ± SD or interquartile range (IQR). Categorical variables were calculated as frequencies and percentages with available data. The differences of 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. The Pearson's chi-square, the Fisher's exact test were performed for unordered categorical variables. The Mann-Whitney U test or the Kruskal-Wallis H tests were 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 diabetes and non-diabetes, and among the patients with no comorbidity, only diabetes and diabetes with comorbidities by log-rank test. Additionally, we didn't 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.

Results

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

The characteristics of this study population at baseline are given in **Table1**.The median age was 54 years old (39-64) and 64 years old (56-70) in the non-diabetes and 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 diabetes group. Systolic blood pressure (SBP) was higher in diabetes group (128mmHg [120-140] vs 124mmHg [119-135]). Moreover, decreased blood oxygen saturation (lower than 93%) occurred more frequently in the diabetes group versus 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 compared to non-diabetes patients.

There were numerous differences of laboratory results between diabetes group and non-diabetes group with COVID-19 (**Table2**). FBG level was significant higher in the diabetes group compared to the non-diabetes group, as expected (9.1 mmol/L [6.5-11.63] vs 5.57 mmol/L [4.92-6.89]), with higher levels of HbA1c (7.87% [6.27-9.03] vs 5.9% [5.4-6.3]). Diabetic patients had higher white blood cell count (WBC) (5.93×10^9/L [4.49-7.53] vs5.35×10^9/L [4.1-6.95]), neutrophil count (NEU) (4.25×10^9/L [3.13-5.37] vs 3.45×10^9/L [2.46-5.07]), neutrophil lymphocyte ratio (NLR) (3.84 [2.45-6.37] vs 2.79 [1.88-4.93]), C-reaction protein (CRP) (29.84mg/L [5.26-75.66] vs 9.1mg/L [1.42-38.95]), lower lymphocyte count (LY)(1.04×10^9/L [0.72-1.43] vs 1.17×10^9/L [0.80-1.61]), compared with non-diabetes group. These results revealed that diabetes represented more severe inflammatory. The percentage of high level in prothrombin time (PT) and D-dimer among diabetes group was higher than that among non-diabetes group. The serum level of albumin (ALB) which was lower in diabetes group (35.7±5.5vs 38.5±5.7) than non-diabetes group. Meanwhile, the Urea nitrogen

(BUN), marker of kidney function, was higher in diabetes group (4.68mmol/L [3.60-6.20] vs 3.90 mmol/L [3.10-5.13]. Non-diabetes participants had significantly lower serum level of lactate dehydrogenase (LDH) (201U/L [160-261] vs 229 U/L [180-341]). 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, between-group comparison with only diabetes group was performed. The baseline characteristic and radiological finding were also summarized in **Table 1**. Diabetes patients with comorbidities were the oldest among three groups . There was a significant difference in blood oxygen saturation, respiratory rate and SBP among three groups but no significant differences in the comparison of non-comorbidity group and only diabetes group or the comparison of diabetes only group and diabetes with comorbidities group. Chest CT scan indicated that diabetes only group had more incidences of bilateral lesions than non-comorbidity group.

Although numerous differences of laboratory findings among non-comorbidity group, diabetes only group and diabetes with comorbidities group (**Table 2**), only ten item had statistical significance between non-comorbidity group and diabetes only group, including ALB (39.3±5.9g/L vs 36.5±6.4)，sodium (140 mmol/L [138,141.00] vs 138 mmol/L [136,141]), BUN(3.70 mmol/L[2.96, 4.66] vs 4.30 mmol/L [3.51, 5.07]), CRP (6.11 mg/L[1.0-27.66]) vs 13.2mg/L[3.0-61.47]), HDL-C (1.11±0.42 mmol/L vs0.97±0.26 mmol/L), certainly embraced FBG (5.37 mmol/L [4.83,6.50] vs 9.4 mmol/L [6.48,11.59]) and HbA1c (5.90% [5.44,6.20] vs 7.60% [5.64,8.98]). Such results combined with oxygen saturation indicated that there was no different in cardiac, liver, lung and coagulation function between both groups.

FBG and HbA1c in diabetes only group and diabetes with comorbidities group were almost at the same level. Compared with diabetes only group, diabetes with comorbidities group had lower LY (0.93 $\times 10^9$/L [0.68-1.33] vs 1.27 $\times 10^9$/L [0.84-1.73]), higher NLR (4.29 [2.62-7.3] vs 3.15 [2.08-5.06]) and CRP (39.9 [6.60-77.67] vs 13.2 [3.0-61.47]), which represented more severe inflammatory response.

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

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

Compared with non-diabetes group, the incidence of severe cases was more prevalent among the diabetes group (34.6% vs 21.7%). However, there were no significant in ICU admission, length of hospital stay and the duration from admission to ICU between both groups. Diabetes group had higher rate of ARDS (11% vs 5.7%) and hypoproteinemia (15% vs 6.5%). As regard other complications, ACI, AKI, secondary infection, shock, no observable difference was identified between diabetes group and non-diabetes group.

Treatment and primary outcome of non-comorbidity group and diabetes only group were no difference (**Table 3**), results for all-cause mortality were similar in both groups (log-rank p=0.59) (**Figure 2B**). As regard the second endpoint, there was no difference between both groups expect hypoproteinemia (5.0% vs 16.9%). Likewise, there was a similar frequency of COVID-19 pharmacological therapy in only diabetes patients versus diabetes with comorbidities patients, however, the latter was more likely to receive mechanical ventilation (10.8% vs 18.3%), had higher incidence of mortality (4.6% vs 18.3%), shock (0 vs 1.6%) and more severe cases (21.5% vs 41.3%). The overall survival rate was lowest in the diabetes with comorbidities group (log-rank p< 0.0001) (**Figure 2B**).

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

Diabetic survivors (n=165) and non-survivors(n=26) had a lot in common of basic characteristic except for decreased blood oxygen saturation (10.9% vs 26.9%) and rapid breathing (18.2% vs 26.9%) which were more frequently in non-survivors (**Table S2**), indicated that the latter had sever lung dysfunction. There were numerous differences of laboratory results between diabetic survivors and non-survivors with COVID-19 that reflected functions of different organs and systems (**Table S2**). Diabetic non-survivors had higher WBC (7.26×10^9/L [5.19-13.07] vs 5.91×10^9/L [4.42-7.29]), NEU (6.22 × 10^9/L [3.69-11.33] vs 4.09 [3.01-5.13]), NLR (10.43 [5.78-16.84] vs 3.50 [2.33-5.53]), CRP (115.3 [66.11-170.6] vs 25.4 [4.44-63.0]), IL-6 (83.47pg/ml [35.75-243.60] vs 3.09pg/ml [1.50-5.25]), lower LY (0.65 × 10^9/L [0.56-1.07] vs 1.08×10^9/L [0.78-1.48]) compare to diabetic survivors, reflecting that mortality patients had severe inflammatory response. Serum levels of PT(14.0s [11.6-15.4] vs 16.2s [13.5-18.9]), D-dimer(0.62mg/L [0.62-1.09] vs 5.40 mg/L [1.50-21.00]), ALT (21.3 U/L [15.3-32.3]vs31.0 U/L [(20.9-46.6]), AST(27.0 U/L[19.0-38.7] vs 43.0 U/L[31.0-60.5]), BUN(4.5

mmol/L [3.59-5.82] vs 6.51 mmol/L[4.92-17.45]), creatinine(64.0 umol/L [44.6-81.0] vs 73.0 umol/L [64.0- 129.6]), CK(61.0 U/L [36.5-111.0] vs 85.0 U/L [71.0-364.0]), LDH(216 U/L [172-219] vs 522 U/L [420-611]), all significantly higher in non-survivors which reflected more severe coagulation, liver, kidney, and cardiac dysfunction. Diabetic non-survivors reported higher average FBG (12mmol/L [9.4-12.81] vs 8.7 mmol/L [6.5-11.36]) compared with survivors.

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

Undoubtedly, higher proportions of occurrence 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, non-survivors group had greater incidence of severe cases (33.7% vs 100%), ICU admission (6.7% vs 42.3%), and more likely to receive corticosteroid (33.3% vs 73.1%). There was a significantly lower frequency of hypoglycemic medication in diabetic non-survivors vs diabetic survivor, including the usage of metformin(30.9 % vs 11.5%),sulfonylurea(21.8%vs 3.8%) and AGI （45.5% vs 7.7%）, which might relate to the blood glucose controlled.

Clinical characteristics, laboratory results, treatment and outcome of diabetic COVID-19 patients using metformin and matched non-metformin user

Of 191 diabetic patients with COVID-19, 54 cases using metformin, after sex, age-matching, there was 50 patients using metformin and sex, age-matched 50 non-metformin user in this part. The frequency of fever (54% versus 78%) and fatigue (38% versus 18%) showed significant differences in clinical characteristics between diabetic COVID-19 patients using metformin and matched non-metformin users (**Table S3**). Laboratory finding (**Table 6**) revealed metformin user had lower level of LDH (237 ±115 U/L vs 304±162 U/L) and FBG (10.57±4.92 mmol/L vs 8.32±2.47 mmol/L), however the distribution of glucose was similar. Results which referred liver, kidney, cardiac, coagulation and inflammatory response were not statistically significant. Primary outcome, secondary outcome of patients who using metformin were comparable to matched non-metformin user (**Table 7**). The former group showed a higher need for antiviral (98% vs 84%), antibiotics (90% vs 74%). Insulin (52.0% vs 20%), sulfonylurea (36.0% vs 2%), AGI (56.0% vs 6%), thiazolidinedione (12% vs 0) were also applied significantly more frequently to the individuals using metformin.

Clinical characteristics, laboratory results, treatment and outcome of diabetic COVID-19 patients using AGI and matched non-AGI user

Of 191 diabetic patients with COVID-19, 77 cases using metformin, after sex, age-matching, there was 46 patients using metformin and sex, age-matched 46 non-metformin user in this part. **Table S3** showed that the length about onset of symptom to hospital admission was longer in AGI group when compared with matched non-AGI group, which indicated that the symptoms in former patient might relatively mild.. Noteworthy, parts of inflammation response related laboratory results, such as WBC (4.83×10^9/L [4.04-6.68] vs 5.91 [4.42-9.35]), NLR(3.25 [2.05-4.41] vs 4.88 [2.50-12.32]), CRP (26.2 [3.7-52.2] vs 63.8[10.8-83.4]) were significant lower in AGI group (**Table 6**). Furthermore, these differences were not related to glucose control as serum level of both groups was comparable.

The mortality rate (2.2% vs 26.1%) was lower in AGI group (**Table 7**), and also the rate of ARDS (2.2%vs 17.4%) and shock (2.2% vs 21.7%). At the same time, patients who treated with AGI indicated a lower need treatment for 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 patient with COVID-19

Among the included 1131 patients, multivariable Cox regression **(Table 8**) showed that male sex (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), CVD (HR 2.35, 95%CI 1.27-4.33) were risk factors for the mortality of COVID-19. Age was also the risk factor for mortality of COVID. However, diabetes alone was not the independent risk factor for mortality of patients with COVID-19.

Discussion

Lots of studies had demonstrated that diabetic patients had higher risk of mortality in COVID, as well as developing more severe cases [2, 4, 11, 12]. Guo et al[12] reported that diabetes was a risk factor for the progression and prognosis of COVID-19. However,

Shi et al pointed out that diabetes was not independently associated with COVID mortality, while commonalities, such as hypertension, cardiovascular disease played more important roles in contributing to the in-hospital death of COVID-19 patients which was relatively limited-sized [13]. In this study which had relatively rich clinical data, we found that diabetes alone was not the independent risk factors for in-hospital mortality of COVID-19, but comorbidities such as hypertension, CKD were risk factors, this result was consistent with the previous study [13]. Partially consistent with the previous studies, our study found that, compared with non-diabetic patients, diabetic COVID-19 patients were older, had worse outcome including higher rate of mortality, severe cases and ARDS, presented severe inflammation response, lung and coagulation dysfunction [2, 11, 12, 14]. Additionally, diabetic patients had increased level of urea nitrogen and decreased level of albumin. These abnormalities indicated that COVID-19 may be associated with progressive organ injury in patients with diabetes. Pre-existing hypertension, CHD, CVD, and CKD had higher frequencies in the diabetic group. Recent studies reported that patients with hypertension cardiovascular, CKD, CVD were more likely to develop severe cases [4, 6, 15-17] , so we compare the diabetic COVID patients without comorbidity and COVID atients without any comorbidity in order to identify if diabetes without comorbidity was a risk factor of COVID-19. In our study, there was no difference in the outcome between non-comorbidity group and diabetes only group. Shi et al reported that even thought COVID-19 patients with diabetes had worse outcomes; diabetes was not independently associated with in-hospital death, which was consistent with our results [16]. Besides, most laboratory results were comparable between non-comorbidity group and diabetes only group except CRP, albumin, sodium, urea nitrogen, HDL-C and, of course blood glucose. As we all known, CRP was an inflammatory biomarker, which was related to glucose homoeostasis, obesity and atherosclerosis [18], and it was independently related to insulin sensitivity [19]. Meanwhile, insulin resistance was a main characteristic of type 2 diabetes, since CRP was related to the chronic inflammatory situation, and the level of WBC, NEU, LY, which reflected the acute infection of disease pathogen, were not statistical significance, we inferred that diabetes itself didn't increase the degree of the inflammation after SARS-CoV2 infection.

Diabetic patients with comorbidities were more serious when compared with diabetes only group and non-comorbidity group. The mortality was higher in diabetes with comorbidities group, but the difference between both diabetes groups had no relation of FPG, because the serum of FPG in both diabetes groups was comparable. Patients of diabetes with comorbidity was 10 years older than the patients who had no comorbidity expect diabetes, furthermore, age ≥65 was associated with greater risk of development of death[4]. As described above, patients with hypertension, CVD were more likely to develop severe cases[4, 16, 17, 20]. Furthermore, our analysis indicated that age, hypertension, CKD, CVD were the risk factors for mortality of COVID-19. Since diabetes with comorbidities group higher prevalence of hypertension, CKD and CVD, it was no doubt that this group had worse outcome than patients who just had diabetes.

One unanticipated result was that AGI, not metformin, could improve prognosis through decreased inflammation degree, which was independent of blood glucose level. In addition, acarbose accounted for 97% of the glycosidase inhibitors used. Feng et al reported acarbose could effectively block the metastasis of enter virus 71(EV71) from the intestine to the whole body [21]. EV71 was one of the main cause of hand-foot-and-mouth disease (HFMD), its infection relied on the interaction of the canyon region of its virion surface and the glycosylation of SCARB2 protein which was the cellular receptor of EV71 infection. Dang et al found that acarbose not only to inhibited cellular receptors of various glycosylated viruses but also competitively blocked the canyon region of EV71 virion surface [22], s, so it blocked the metastasis of EV71 from the intestine. Angiotensin converting enzyme II (ACE2) was SARS-CoV2 cell entry receptor [23], glycosylation sites play an important role in the combination of SARS-CoV2 and its receptor[24, 25]. Chloroquine was reported that blocked SARS-CoV infection through interfering with the glycosylation of cellular receptors [26]. As previously stated, acarbose inhibited glycosylation of EV71 receptors, meanwhile, diabetic COVID-19 patient who was treated with acarbose had better outcome than the patients who wasn't treated, it can thus be suggested that acarbose could improve prognosis of COVID-19 infection by inhibited the glycosylation of ACE2. In addition, compared to the non-AGI group, the lower level of WBC, NLR, and CRP in AGI group which means decreased inflammatory response and further supported the anti-SARS-CoV2 function of acarbose. Furthermore, previous study showed that acarbose could change gut microbiota, then beneficially regulates the body's immune function [27]. Recent study revealed that fetal microbiomes change was happened in COVID-19 patients, characterized by depletion of beneficial commensals, and enrichment of opportunistic pathogens[28]. Therefore, we inferred that acarbose might increase the baseline abundance of microbiota which had inversely correlated with COVID-19.

As previous studies reported that metformin has multiple additional health benefits in diabetic patients [29-31], we anticipated that metformin would improve prognosis after COVID-19 suffering, however, the results was unexpectedly. Scanning the literature, we found that metformin improves ACE2 stability through AMPK [32], which means metformin may increase ACE2 availability. In

addition, the median level of FBG was higher in metformin users than non-users, as previous study reported that improving glycemic control substantially reduced the risk of mortality for COVID-19.

The study has some limitations. Firstly, due to the retrospective and multiple-center study design, some information, such as patients' exposure history, diabetes medication and several laboratory items were not available for all patients. Secondly, samples were only from Hubei province, China, thus more studies in other regions even other countries might get a more comprehensive insight of COVID-19. However, this study is one of the largest retrospective and multicenter studies among patients with COVID-19. Additionally, this study is one the first study to investigate the influence of diabetes medications in diabetic patients with COVID-19. The relatively aplenty clinical data and numerous events also strengthen the results. The conclusion will help clinicians to identify high-risk patients and choose suitable diabetes medication for diabetic patients.

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

Declarations

Competing interests: We declare no competing interests.

Ethics approval and consent to participate: 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, institutional Ethics Commission of the Fifth Affiliated Hospital of Sun Yat-sen University. Written informed consent was waived by the Ethics Commission of the hospitals for emerging infectious diseases.

Consent for publication: Not applicable.

Availability of data and materials: The data used and/or analyzed during this study are available from the corresponding author on request.

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Authors contributions

HL and JM 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. SL and WH drafted the manuscript. ZL and SL did the analysis. QC, YX, WH, CL, LW, ZC, LR, JY and MY collected the data, ZL, JY, SC and JT recorded the data.

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Tables

Table 1. Baseline characteristics of 1331 COVID-19 patients divided into different groups

	Total (n=1331)	Non-diabetes (n=1140)	Diabetes (n=191)	*P*# value	Non-comorbidity (n=779)	Diabetes only (n=65)	Diabetes with comorbidities (n=126)	*P*† 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, years	56.0 (42.0-65.0)	54.0 (39.0-64.0)	64.0 (56.0-70.0)	**<0.001**	48.0*** (36.0-60.0)	57.0 (50.0-64.0)	67.0*** (59.0-72.0)	**<0.001**
18-49	500(37.6)	477 (41.8)	23 (12.0)	**<0.001**	415 (53.3)***	16 (24.6)	7 (5.6)***	**<0.001**[a]
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**
SBP, mmHg	125(120-135)	124(119-135)	128(120-140)	**0.001**	121(118-131)	127 (120-133)	130(120-140)	**<0.001**

DBP, 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)*	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	-	-	-	-

Datas are expressed as n (%), mean ± SD or median (IQR). *P* values were calculated by T Test, Mann-Whitney U test, x^2 test, Fisher's exact test, One-Way ANOVA, Kruskal-Wallis H test as appropriate. [a] Mann-Whitney U test comparing all subcategories. [#]Comparing groups of diabetes and non-diabetes patients; †Comparing groups of non-comorbidity, only diabetes and diabetes with comorbidities. Compared with diabetes only group, **P*<0.05, ***P*<0.05, ****P*<0.001. SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, Coronary heart disease; CVD, cerebrovascular disease; CKD, Chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Table 2. Laboratory results of 1331 COVID-19 patients divided into different groups

	Total (n=1331)	Non-diabetes (n=1140)	Diabetes (n=191)	*P*# value	Non-comorbidity (n=779)	Diabetes only (n=65)	Diabetes with comorbidities (n=126)	*P*† value
WBC, ×109 per 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, × 10⁹ per 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, × 10⁹ per 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) **	**<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) *	**<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**	<**0.001**
PLT, × 10⁹ per 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) *	13.2(3.0-61.5)	39.9 (6.6-77.7) *	**<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) **	**<0.001**
≤0.5	555 (52.5)	497 (55.0)	58 (37.9)	**<0.001**	386 (63.4)	27 (50.9)	31 (31.0) **	**<0.001**[a]
>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***	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) *	**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)*	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)*	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)	**<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) *	**<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) *	**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*	**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*	**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*	0.97±0.26	0.92±0.27	**<0.001**
FBG, 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) ***	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) ***	17 (29.8))	26 (26.3)	**<0.001[a]**
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) **	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, x^2 test, Fisher's exact test, One-Way ANOVA or Kruskal-Wallis H test as appropriate. [a] Mann-Whitney U test comparing all subcategories. [#]Comparing groups of diabetic and non-diabetic patients; †Comparing groups of non-comorbidity, only diabetes and diabetes with comorbidities. Compared with diabetes only group: *P<0.05, **P<0.05, ***P<0.001. WBC, white blood cell; NEUT, neutrophil ; LY, lymphocyte ; NLR,

neutrophil lymphocyte ratio; Hb, hemoglobin; PLT, platelet; PCT, procalcitonin; CRP, C reactive protein; PT, prothrombin time ; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase ; ALP, alkaline phosphatase ; TBIL, total bilirubin ; BUN, urea nitrogen ; UA, uric acid ; CK, creatine kinase ; LDH, lactate dehydrogenase ; Hs-cTnI, hypersensitive troponin I ; TG, triglyceride; TCH, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin.

Table 3. Treatments and outcomes of 1331 COVID-19 patients divided into different groups

	Total (n=1331)	Non-diabetes (n=1140)	Diabetes (n=191)	*P*# value	Non-comorbidity (n=779)	Diabetes only (n=65)	Diabetes with comorbidities (n=126)	*P*† 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)*	**<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)*	0.706
Hypoproteinemia <30g/l	99(7.7)	71(6.5)	28(15.0)	**<0.001**	38(5.0)***	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, x^2 test, Fisher's exact test, One-Way ANOVA or Kruskal-Wallis H test as appropriate. #Comparing groups of diabetic and non-diabetic patients;

†Comparing groups of non-comorbidity, only diabetes and diabetes with comorbidities. Compared with diabetes only group: *P<0.05, **P<0.05, ***P<0.001. ARDS, acute respiratory distress syndrome; ACI, acute cardiac injury; AKI, acute kidney injury.

Table 4. Laboratory results of diabetic survivors and non-survivors with COVID-19

	Total (n=191)	Survivors (n=165)	Non-survivors (n=26)	*P* value
WBC, ×109 per L	5.94(4.49-7.53)	5.91(4.42-7.29)	7.26(5.19-13.07)	**0.016**
NEUT, × 10 per L	4.25(3.13-5.37)	4.09(3.01-5.13)	6.22(3.69-11.33)-	**<0.001**
LY, × 10 per 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 per 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**[a]
>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
BUNmmol/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
FBG, 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[a]
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, x^2 test, or Fisher's exact test, as appropriate. [a] Mann-Whitney U test comparing all subcategories. *P,* comparing groups of diabetic survivors and non-survivors. WBC, white blood cell; NEUT, neutrophil ; LY, lymphocyte ; NLR, neutrophil lymphocyte ratio; Hb, hemoglobin; PLT, platelet; PCT, procalcitonin; CRP, C reactive protein; PT, prothrombin time ; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase ; ALP, alkaline phosphatase ; TBIL, total bilirubin ; BUN, urea nitrogen ; UA, uric acid ; CK, creatine kinase ; LDH, lactate dehydrogenase ; Hs-cTnI, hypersensitive troponin I ; TG, triglyceride; TCH, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1C, glycosylated Hemoglobin.

Table 5. Treatments and outcomes of diabetic survivors and non-survivors with COVID-19

	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
AGI	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 <30g/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, days	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, x2 test, or Fisher's exact test, as appropriate. Comparing groups of diabetic survivors and non-survivors. AGI, Alpha-glucosidase inhibitor; ARDS, acute respiratory distress syndrome; ACI, acute cardiac injury; AKI, acute kidney injury

Table 6. Laboratory results of diabetic COVID-19 patients using metformin or AGI and matched non-metformin or non-AGI inhibitor user

	Metformin (n=50)	Matched non-Metformin (n=50)	AGI (n=46)	Matched non-AGI (n=46)
WBC, ×109 per L	6.33±2.25	6.27±2.62	**4.83(4.04,6.68)**	**5.91 (4.42,9.35) #**
NEUT, × 10 per 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 per 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) ##**
Hb, g/L	126.0±15.7	126.5±14.9	126.0±16.9	129.3±17.3
PLT, ×10 per 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) #**
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***	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***	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
FBG, mmol/L	**10.57±4.92**	**8.32±2.47****	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). Comparison of metformin users and non-users: *P<0.05, **P<0.01, ***P<0.001. Comparison of AGI users and non-users:: $^{\#}P$<0.05, $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.05. AGI, alpha-glucosidase inhibitor; WBC, white blood cell; NEUT, neutrophil ; LY, lymphocyte ; NLR, neutrophil lymphocyte ratio; Hb, hemoglobin; PLT, platelet; PCT, procalcitonin; CRP, C reactive protein; PT, prothrombin time ; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase ; ALP, alkaline phosphatase ; TBIL, total bilirubin ; BUN, urea nitrogen ; UA, uric acid ; CK, creatine kinase ; LDH, lactate dehydrogenase ; Hs-cTnI, hypersensitive troponin I ; TG, triglyceride; TCH, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin.

Table7. Treatments and outcomes of diabetic COVID-19 patients using metformin and matched non-metformin, AGI and matched non-AGI

	Metformin (n=50)	Matched non-Metformin (n=50)	AGI (n=46)	Matched non-AGI (n=46)
Treatments				
Antiviral therapy	**49(98.0)**	**42(84.0)***	41(89.1)	43(93.5)
Antibiotic therapy	**45(90.0)**	**37(74.0)***	40(87.0)	40(87.0)
systemic glucocorticoids	17(34.0)	16(32.0)	**12(26.1)**	**22(47.8)#**
Intravenous immunoglobulin	15(30.0)	11(22.0)	**11(23.9)**	**22(47.8)#**
Renal replacement therapy	0(0.0)	1(2.0)	0(0.0)	0(0.0)
Insulin	**26(52.0)**	**10(20.0)****	**23(50.0)**	**39(84.8)###**
Metformin	50	0	21(45.7)	15(32.6)
Sulfonylurea	**18(36.0)**	**1(2.0)*****	**17(37.0)**	**8(17.4)#**
DPP-4 inhibitor	3(6.0)	0(0.0)	3(6.5)	3(6.5)
AGI	**28(56.0)**	**3(6.0)*****	46(100.0)	0(0.0)
thiazolidinedione	**6(12.0)**	**0(0.0)***	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)#**
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)#**
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)#**
Hypoproteinemia <30g/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, days	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)##**
Death	3(6.0)	9(18)	**1(2.2)**	**12(26.1)**

Data are expressed as n (%), mean ± SD or median (IQR). Comparison of metformin users and non-users: *P<0.05, **P<0.01, ***P<0.001. Comparison of AGI users and non-users:: #P<0.05, ##P<0.01, ###P<0.05. AGI, alpha-glucosidase inhibitor; ARDS, acute

respiratory distress syndrome; ACI, acute cardiac injury; AKI, acute kidney injury

Table 8. Multivariate COX regression analysis on the risk factors associated with mortality of 1331 COVID-19 patients

Factor	Hazard ratio	*P* value
Sex (male)	2.59(1.68-3.99)	<0.001
Age		
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.

Figures

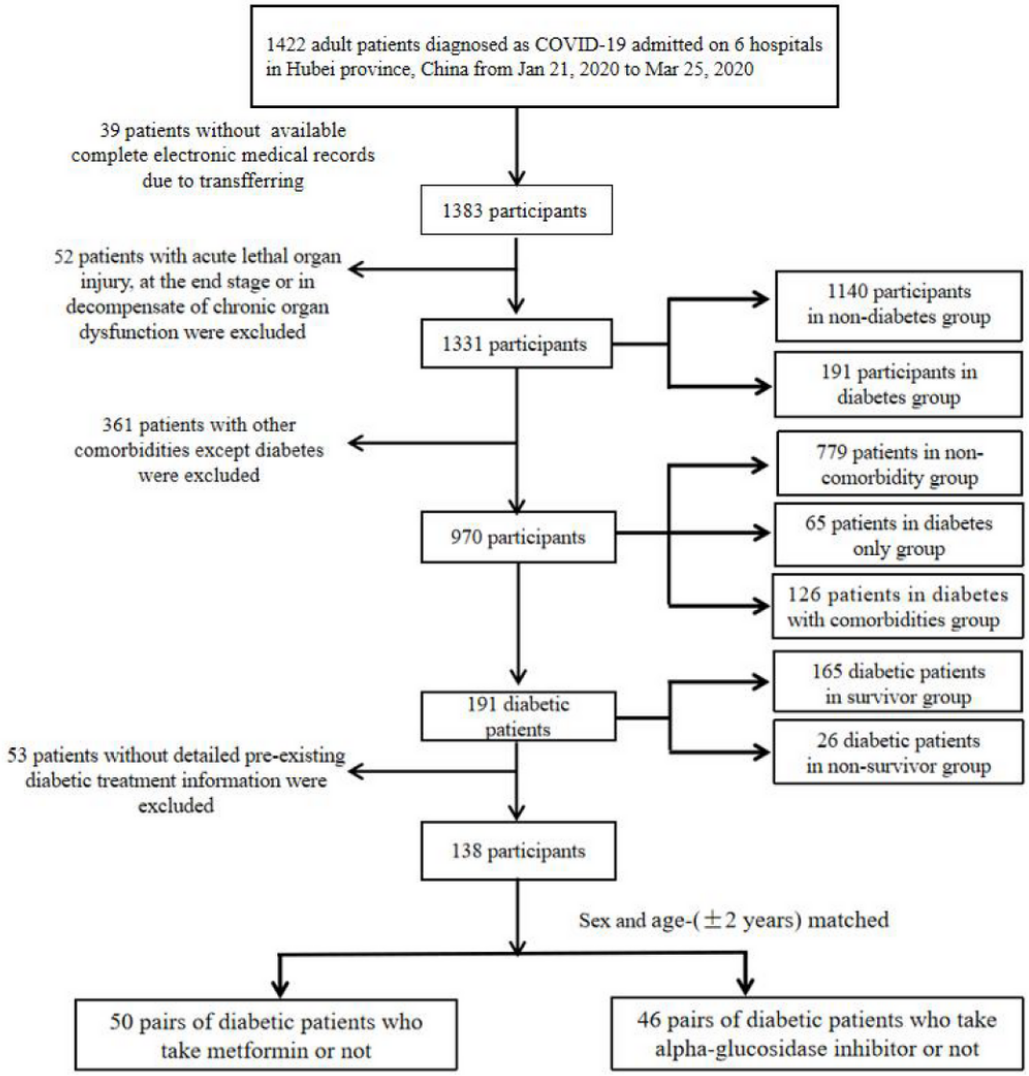

Figure 1

Flow chart of patient recruitment.

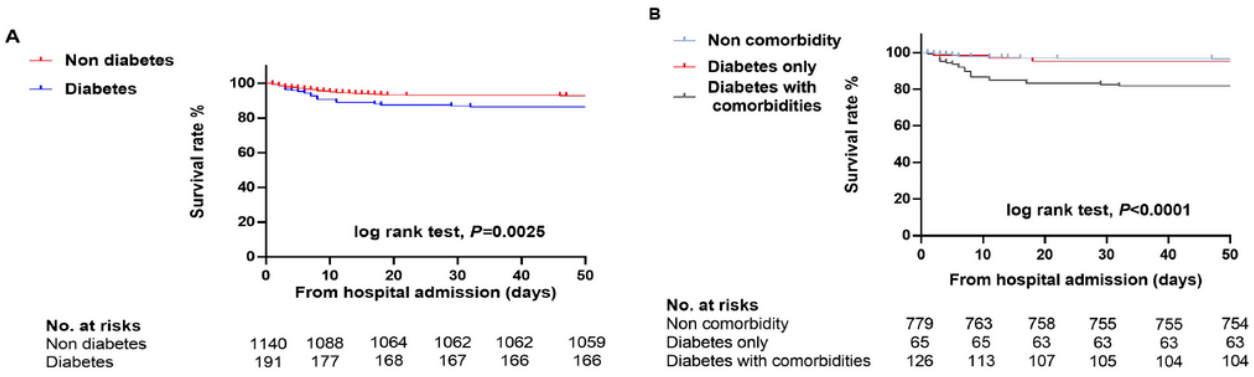

Figure 2

Kaplan-Meier survival curves of in-hospital mortality among patients with COVID-19. A, Kaplan-Meier survival curves for in-hospital mortality between diabetes and non-diabetes from hospital admission. B, Kaplan-Meier survival curves in-hospital mortality comparison of patients with non-comorbidity, diabetes only and diabetes with comorbidities from hospital admission. Compared patients with non-comorbidity and diabetes only from hospital admission (Log rank test, p=0.590). Compared patients with only-diabetes group and diabetes with comorbidities from hospital admission (Log rank test, p=0.009).

Supplementary Files

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