Diabetes, even newly defined by HbA1c testing, is associated with an increased risk of in-hospital death in adults with COVID-19

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Diabetes, even newly defined by HbA1c testing, is associated with an increased risk of in-hospital death in adults with COVID-19

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Abstract

Aims: Diabetes is associated with poor coronavirus disease 2019 (COVID-19) outcomes. However, little is known on the impact of undiagnosed diabetes in the COVID-19 population. We investigated whether diabetes, particularly undiagnosed diabetes, was associated with an increased risk of death from COVID-19.

Methods: This retrospective study identified adult patients with COVID-19 admitted to Tongji Hospital (Wuhan) from January 28 to April 4, 2020. Diabetes was determined using patients' past history (diagnosed) or was newly defined if the hemoglobin A1c (HbA1c) level at admission was 6.5% (≥ 48 mmol/mol) (undiagnosed). The in-hospital mortality rate and survival probability were compared between the non-diabetes and diabetes (overall, diagnosed, and undiagnosed diabetes) groups. Risk factors of mortality were explored using Cox regression analysis.

Results: Of 373 patients, 233 were included in the final analysis, among whom 80 (34.3%) had diabetes: 44 (55.0%) reported a diabetes history, and 36 (45.0%) were newly defined as having undiagnosed diabetes by HbA1c testing at admission. Compared with the non-diabetes group, the overall diabetes group had a significantly increased mortality rate (22.5% *vs* 5.9%, p <0.001). Moreover, the overall, diagnosed, and undiagnosed diabetes groups displayed lower survival probability in the Kaplan-Meier survival analysis (all p <0.01). Using multivariate Cox regression, diabetes, age, quick sequential organ failure assessment score, and D-dimer ≥ 1.0 μg/mL were identified as independent risk factors for in-hospital death in patients with COVID-19.

Conclusions: The prevalence of undiagnosed pre-existing diabetes among patients with COVID-19 is high in China. Diabetes, even newly defined by HbA1c testing at admission, is associated with increased mortality in patients with COVID-19. Screening for undiagnosed diabetes by HbA1c

measurement should be considered in adult Chinese inpatients with COVID-19.

Keywords: Coronavirus disease 2019; Undiagnosed diabetes; Hemoglobin A1c; Mortality

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], has spread worldwide, resulting in more than 30 million confirmed infections and over one million deaths as of September 30, 2020 (see https://covid19.who.int) [2].

The reported mortality rate for hospitalised patients with COVID-19 ranges from 1.4% to 22.5%, which may be due to different characteristics of patient populations, such as age, comorbidities, and the availability of medical resources [3-6]. Studies have shown that elderly patients with underlying comorbidities are at a greater risk of poor outcomes [7-9]. In particular, several studies have highlighted the association between diabetes and poor COVID-19 prognosis. Diabetes is a common comorbidity, and more patients with severe cases of COVID-19 have diabetes than patients with mild symptoms [8, 10-12]. Diabetic patients also have a higher mortality rate than non-diabetic patients [13-15]. However, the diagnostic rate of diabetes is currently low, particularly in China [16], leaving many patients undiagnosed and untreated. There is little information on the prevalence of undiagnosed diabetes in the COVID-19 population and whether undiagnosed diabetes is associated with an increased risk of death from COVID-19.

In this retrospective observational study, we described the prevalence of diabetes, including previously diagnosed and undiagnosed diabetes, in hospitalised patients with COVID-19 at a tertiary medical centre in Wuhan, China. Moreover, we investigated whether diabetes, particularly undiagnosed

diabetes, was associated with an increased risk of in-hospital death in patients with COVID-19.

Research Design and Methods

Study Design and Population

This retrospective study aimed to investigate the impact of diabetes on the prognosis of COVID-19. We screened all adult patients with a confirmed diagnosis of COVID-19 who were admitted to the COVID-19 wards at Zhongfaxincheng campus of Tongji Hospital in Wuhan, China, from January 28, 2020 to April 4, 2020. COVID-19 was diagnosed by testing for SARS-CoV-2 using quantitative polymerase chain reaction assays of nasopharyngeal samples, according to the guideline for COVID-19 issued by the Chinese National Health Committee (version seven) [17]. Disease severity classification and treatment protocol were also based on this guideline. In Wuhan, critical, severe, and most moderate patients with COVID-19 were directly admitted to tertiary medical centres such as our institution. Mild patients and a few moderate patients were treated in Fangcang temporary shelter hospitals [18]. If the disease progressed, patients were transferred to tertiary medical centres for further treatment. We excluded transferred patients from Fangcang hospitals to eliminate bias associated with pre-admission treatments. We also excluded patients who lacked key variables (history record, vital signs, routine blood and glucose test data) or had other serious comorbidities (end-stage renal disease or diseases requiring corticosteroid or immunosuppressant therapy) in the final analysis (Fig. 1).

This study was approved by the Ethics Commission of Peking University Third Hospital (IRB 00006761-M2020060).

Data Abstraction

Using a standardised data collection form, the epidemiological records, demographic data, clinical

manifestations, laboratory findings, treatment, and outcome data of patients with COVID-19 were extracted from electronic medical records. All data were collected as of April 4, 2020 and were independently checked by two physicians, and a third researcher adjudicated any difference in interpretation between the two physicians.

Quick sequential organ failure assessment (qSOFA) scores were calculated based on systolic blood pressure, respiratory rate in room air, and mental status at admission [19]. Laboratory findings included first in-hospital routine blood test, liver and kidney function test, fasting plasma glucose and hemoglobin A1c (HbA1c) levels, coagulation profile, and inflammatory markers. HbA1c testing was performed by high-performance liquid chromatography (HA-8180, Arkray; Kyoto, Japan).

Definition of Diabetes

Diabetes was determined based on self-reported diabetes history. If patients denied having a history of diabetes and their HbA1c levels at admission were 6.5% (≥ 48 mmol/mol) without hemoglobinopathy, they were established to have diabetes.

Statistical Analyses

All statistical analyses were performed using SPSS Statistics (version 23.0, IBM; Armonk, NY). Graphs were conducted with R software (version 4.0.2, R Foundation). The normality of distributions of continuous variables was checked by the Kolmogorov-Smirnov test. Data that were not normally distributed are expressed as medians and interquartile ranges (IQRs). Categorical variables are presented as numbers and percentages (%). Comparisons between groups were analysed using the Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. Clinical features and 28-day

all-cause mortality during hospitalisation were analysed and compared between non-diabetic and diabetic patients. Cumulative survival rates were plotted by the Kaplan-Meier method with the log-rank test. Risk factors associated with in-hospital death and their corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) were analysed using univariable and multivariable Cox regression analyses (likelihood ratio method). Sensitivity analysis was performed in a subgroup of patients with HbA1c results at admission, and risk factors for in-hospital death were also evaluated with logistic regression analysis. A two-sided *P* value < 0.05 was considered statistically significant.

Results

Clinical Characteristics of Patients at Admission

Of the 373 patients with COVID-19, 101 patients transferred from Fangcang hospitals were excluded. An additional 39 patients were excluded because of missing key variables (30 cases) or end-stage renal disease (six cases), renal transplantation (two cases), and systemic lupus erythematosus under continuous corticosteroid therapy (one case). In total, 233 patients were included in the final analysis. Eighty (34.3%) patients had diabetes, among whom 44 (55.0%) were previously diagnosed and 36 (45.0%) were newly defined as having undiagnosed diabetes with an HbA1c level ≥ 6.5% (48 mmol/mol) at admission (Fig. 1). Based on the physicians' clinical evaluation, type 1 diabetes was not observed.

The demographic and clinical characteristics and laboratory findings of patients with COVID-19 at admission are presented in Table 1. The median age was 64 years, and there were 115 (49.4%) males. The most common comorbidities other than diabetes were hypertension (90 cases, 38.6%), coronary artery disease (26 cases, 11.2%), and cerebrovascular disease (12 cases, 5.2%). At admission, 115 (49.4%), 95 (40.8%), and 23 (9.8%) patients were classified as moderate, severe, and critical cases,

respectively.

The median age was higher in diabetic patients than in non-diabetic patients, and diabetic patients also had a higher rate of pre-existing hypertension and coronary artery disease. More patients in the diabetic group were classified as having severe and critical cases than those in the non-diabetic group. No significant difference was found between groups in sex, other comorbidities, or qSOFA score at admission. Diabetic patients had higher fasting plasma glucose and HbA1c levels, higher white blood cell counts, lower lymphocyte counts, and higher serum creatinine and D-dimer levels than non-diabetic patients at admission (Table 1).

In the subgroup analysis, patients with undiagnosed diabetes had more comorbid chronic pulmonary diseases, higher qSOFA scores, more severe and critical cases, higher fasting plasma glucose and HbA1c levels, higher white blood cell counts, and higher serum creatinine and D-dimer levels than those without diabetes at admission (Supplementary Table 1).

In-hospital Mortality Rate

Twenty-seven patient deaths occurred during hospitalisation, all within 28 days after admission. The in-hospital mortality rate was higher in the overall (22.5% *vs.* 5.9%, p <0.001), diagnosed (22.7% *vs.* 5.9%, p =0.001), and undiagnosed diabetes (22.2% *vs.* 5.9%, p =0.002) groups than in the non-diabetic group (Table 1, Supplementary Table 1). The mortality rate did not significantly differ between patients with undiagnosed and diagnosed diabetes (22.2% *vs.* 22.7%, p =0.957). The survival curves of diabetic and non-diabetic patients with COVID-19 are shown in Fig. 2a, indicating that the survival probability was lower in diabetic patients than in non-diabetic patients. Moreover, the probability of survival was significantly decreased in patients with both diagnosed and undiagnosed diabetes compared to those

without diabetes (Fig. 2b and c). In a subgroup of 140 patients who had their HbA1c level tested, the survival probability was still lower in patients in the overall, diagnosed, and undiagnosed diabetes groups than in the non-diabetic group (Supplementary Fig. 1).

Risk Factors Associated with In-hospital Death in Patients with COVID-19

To further investigate whether diabetes was independently associated with an increased risk of mortality in patients with COVID-19, Cox regression analysis was performed. Using univariable analysis, it was found that the risk of in-hospital death was significantly increased in all patients with diabetes (HR 3.80, 95% CI 1.71–8.47), those with diagnosed diabetes (HR 4.03, 95% CI 1.64–9.91), and those with undiagnosed diabetes who were newly defined by HbA1c testing at admission (HR 1.89, 95% CI 1.18–3.05) compared to those without diabetes. Age, qSOFA score, white blood cell count, lymphocyte count, fasting plasma glucose level, and D-dimer level ≥1 μg/mL at admission were also significantly associated with the risk of in-hospital death (Table 2).

Subsequently, we used age, diabetes, qSOFA score, lymphocyte count, and high D-dimer level as variables for multivariable Cox regression analysis. In addition, male sex and chronic pulmonary disease, which both reached 10% significance in the univariable analysis, were also included. A total of 223 patients with complete data for all analysed variables were included in the multivariable Cox regression model. Age (HR 1.07, 95% CI 1.02–1.10), diabetes (HR 2.64, 95% CI 1.14–6.11), qSOFA score (HR 2.80, 95% CI 1.58–4.97), and D-dimer level ≥1 μg/mL (HR 3.28, 95% CI 1.12–9.64) at admission were independently associated with an increased risk of in-hospital death in patients with COVID-19 (Table 2). Results of the multivariable logistic regression analysis were consistent with those of the Cox regression analysis (Supplementary Table 2).

Discussion

In this retrospective observational study, the prevalence of diabetes in patients with non-mild COVID-19 cases was 34.3%. Among the diabetic patients, 45.0% were unaware of their underlying diabetes condition before admission. Diabetes was independently associated with an increased risk of in-hospital death in patients with COVID-19. Notably, patients with undiagnosed diabetes who were newly defined by HbA1c testing at admission had an increased risk of mortality during hospitalisation similar to that of patients with diagnosed diabetes, compared with their non-diabetic counterparts.

Diabetes has been garnering attention in terms of its prevalence and impact in the COVID-19 population. A report on the largest case series of COVID-19 in China, conducted by the Chinese National Emergency Response Epidemiology Team, showed that the prevalence of diabetes among 44,672 confirmed Chinese mainland patients with COVID-19 was 5.3% [20]. Observational studies and meta-analyses reported that the prevalence of pre-existing diabetes in Chinese patients with COVID-19 ranged from 8.2% to 19.0% [8, 21-23]. Here, we showed a much higher prevalence of diabetes (34.3%) in patients with COVID-19. This could be due to two reasons. First, our patients were from one of the national intensive care centres for COVID-19 that only admitted moderate to critical patients. The patients in our study were older and had more severe conditions than those in the nationwide analysis [20, 21]. Therefore, a higher prevalence of diabetes was expected in this study, similar to that reported by medical centres in Western countries [6, 11, 24, 25]. This might also suggest an association between pre-existing diabetes and an increased severity of COVID-19. Second, we included patients with newly diagnosed diabetes defined by HbA1c testing at admission. By contrast, most previous studies reported the prevalence of diabetes as a comorbidity according to patient histories of those with COVID-19, and patients who were included in non-diabetic groups had no

available HbA1c data [23] or some of them had HbA1c levels over 6.5% [10]. In the most recent national epidemiological survey involving 75,880 adult participants, the prevalence of overall, self-reported, and newly diagnosed diabetes based on the American Diabetes Association criteria were 12.8%, 6.0%, and 6.8%, respectively, in China [26]. In agreement with that study, we found that approximately 50% of diabetic patients (elevated HbA1c levels) were undiagnosed before admission. HbA1c was first introduced into the American Diabetes Association diagnostic criteria of diabetes in 2010 [27]. HbA1c testing can well represent average blood glucose levels within 2–3 months before testing and is not influenced by factors such as acute infection, stress, or recent medications that could alter glucose metabolism, like corticosteroids. Moreover, HbA1c testing does not require fasting. Therefore, HbA1c is a reasonable diagnostic parameter for the quick identification of the background glucose metabolic state in severe and critical patients with COVID-19. Because diabetes is one of the most common comorbidities in patients with COVID-19 and is associated with poor outcomes, HbA1c testing at admission can provide important information for patient assessment and help identify those who have not been diagnosed but are at great risk.

It has been shown that diabetic patients have poorer COVID-19 outcomes. The prevalence of diabetes is much higher in patients with COVID-19 treated in intensive care units than in those treated in general wards [5]. Diabetic patients with COVID-19 had a higher risk of developing severe or critical illness [23] and having multiple-organ damage, and a higher mortality rate than non-diabetic patients [10, 11, 14, 15, 20]. Similar to previous studies [8, 21], our data indicated that diabetes, together with advanced age, a high qSOFA score, and coagulation disorders, was a risk factor for in-hospital death in moderate to critical patients with COVID-19. Similarly, diabetes was also previously reported as a major risk factor for mortality in severe acute respiratory syndrome in 2003

and Middle East respiratory syndrome [28, 29]. Thus far, there is no established effective therapy for reducing the mortality rate of COVID-19. However, a recent study reported that a well-controlled blood glucose level in diabetic patients during hospitalisation was associated with a markedly reduced mortality from COVID-19, in comparison with poorly controlled glycaemia [10]. Therefore, identifying undiagnosed diabetes provides awareness of the background glycaemic disorder, thereby facilitating appropriate intervention for at-risk patients with coronavirus infections, including glucose monitoring and glycaemic control, and possibly better outcomes.

The underlying mechanism of the impact of diabetes on the prognosis of COVID-19 is still under investigation. The dysregulated immune response caused by diabetes may contribute to increased disease severity. Diabetic patients with COVID-19 have more neutrophils and a higher rate of lymphopenia [10], which is in agreement with our findings of higher white blood cell counts and lower lymphocyte counts in diabetic patients than in non-diabetic patients. In addition, diabetes may cause a chronic inflammatory state, elevating the levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and IL-6, and further aggravate cytokine storms in some patients with COVID-19 [30, 31]. However, our study did not show a significant difference in serum IL-6 levels between groups. Angiotensin-converting enzyme 2 (ACE2) may be another underlying mechanism for the detrimental effects of diabetes on the prognosis of COVID-19. SARS-CoV-2 gains entry into host pneumocytes by binding to ACE2 [32]. Diabetic patients were reported to have a higher expression of ACE2, thereby facilitating viral uptake and increasing the risk of severe infection [33]. Moreover, glucose can also directly increase the viral load and upregulate the expression of ACE2 and IL-1β in SARS-CoV-2-infected monocytes in a dose-dependent manner, suggesting that individuals with elevated circulating glucose levels may be more susceptible to SARS-CoV-2 infection and more likely

to develop severe illness [34]. Therefore, the cause for worse prognosis in diabetic patients with COVID-19 is multifactorial [35].

Our study has several advantages. This is the first investigation focusing on the clinical outcomes of both undiagnosed and diagnosed diabetes in patients with COVID-19. The HbA1c determination method used in our center is comparable to the National Glycohemoglobin Standardisation Programme standard. By testing the HbA1c level at admission, we reduced the omission diagnostic rate of diabetes and prevented the overdiagnosis of diabetes because of stress-induced hyperglycaemia. The high percentage of undiagnosed diabetes, together with the similarly worse clinical outcome of undiagnosed and diagnosed diabetes compared with non-diabetes, highlighted the importance of screening for undiagnosed diabetes by HbA1c detection in patients with COVID-19. Moreover, the patients included in this study were admitted at a single medical centre and underwent treatments following uniform clinical guidelines, thereby reducing bias resulting from different treatment methods. Finally, we presented survival curves of diabetic and non-diabetic patients with COVID-19, while most previous studies only showed final outcomes without time-kinetic changes. Shi et al. [23] reported survival curves of patients with COVID-19, in which the survival probability of patients with diabetes was lower than that of sex- and age-matched patients without diabetes. However, in their study, patients in the non-diabetic control group had no available HbA1c data, and the fasting glucose levels in some cases were over 11.1 mmol/L, indicating a high possibility of patients with undiagnosed diabetes in the control group.

Our study has some limitations. First, it was a single-centre study with a limited number of patients. We enrolled as many patients as we could and excluded patients who were transferred from Fangcang hospitals to reduce bias from pre-admission treatment. Second, not all patients had their HbA1c level

tested at admission, particularly those in the non-diabetic group, as not all medical teams in our COVID-19 wards had members specialising in endocrinology. At the very beginning of the pandemic in Wuhan, some medical staff had not realised the potential benefit of evaluating and managing glucose metabolism in patients with COVID-19. Therefore, some patients did not undergo HbA1c testing; thus, the prevalence of diabetes in our COVID-19 population may even be higher than what we reported in this study. Nevertheless, in the subgroup analysis of 140 patients with available HbA1c data, the association between lower survival probability and diabetes (overall, diagnosed, or undiagnosed diabetes) was consistent with the results of the primary analysis of all 233 patients. Third, we only included IL-6 in the risk factor analysis and did not analyse other inflammatory biomarkers, such as serum C-reactive protein (CRP) or ferritin, in the present study. Most patients were tested for high-sensitivity CRP (hsCRP), rather than CRP, because hsCRP was incorporated into the biochemical analysis at our medical centre. hsCRP levels are more associated with systemic low-grade inflammation than with acute inflammatory conditions, such as COVID-19. In addition, IL-6, which is upstream of CRP as a sensitive marker for acute infection, was tested in most of our patients at admission. Therefore, we used IL-6 as the inflammatory biomarker in our Cox regression analysis. Although ferritin data were available in 223 patients, many were tested several days after admission, indicating that the levels could be confounded by other in-hospital factors. Thus, ferritin was excluded in the final analysis.

Conclusion

The prevalence of diabetes is high (34.3%) in adult patients with non-mild COVID-19 cases in China, with 45.0% of the patients being unaware of their underlying diabetes condition. Importantly,

similar to patients with diagnosed diabetes, patients with undiagnosed diabetes are also at a higher risk of in-hospital death from COVID-19. Therefore, HbA1c testing should be considered for all adult inpatients with COVID-19 to help clinicians identify patients with undiagnosed diabetes and provide appropriate management for this potentially high-risk population, including glucose monitoring and glycaemic control, in order to achieve better outcomes.

Declarations

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Conflicts of interest The authors declare that they have no competing interest.

Availability of data and material The dataset analysed during the current study is available from the corresponding author on reasonable request.

Authors' contributions Ye Liu, Ran Lu and Tianpei Hong contributed to the study conception and design. Data collection, analysis and interpretation were performed by Ye Liu, Junhong Wang, Qing Chen, Ruitao Zhang, Shuisheng Zhang, Yunyi Le, Wenhua Xiao and Lin Zeng. The first draft of the manuscript was written by Ye Liu, Ran Lu and Haining Wang. Critical manuscript revision was

performed by Hongwei Gao and Tianpei Hong. All authors read and approved the final manuscript.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Commission of Peking University Third Hospital (IRB 00006761-M2020060).

Consent to participate and publish Because COVID-19 is an emerging infectious disease, the requirement for written informed consent was waived by the Ethics Commission. Moreover, this study analyzed deidentifed participant data for which formal consent is not required.

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Table 1 Demographic, clinical, and laboratory characteristics at admission, and in-hospital death in patients with COVID-19

	Total (n=233)	**Non-diabetes** (n=153)	**Diabetes** (n=80)	**Diabetes *vs* Non-diabetes**	***χ2 or Z***	***p* value**
Demographic and clinical characteristics						
Age (years)	64.0 (52.0–71.0)	64.0 (47.0–69.5)	66.0 (58.0–72.0)	2.0	2.530	0.011
Sex					0.175	0.676
Male	115 (49.4%)	74 (48.4%)	41 (51.3%)	2.9%		
Female	118 (50.6%)	79 (51.6%)	39 (48.7%)	–2.9%		
Comorbidities						
Hypertension	90 (38.6%)	47 (30.7%)	43 (53.8%)	23.1%	11.754	0.001
Coronary artery disease	26 (11.1%)	12 (7.8%)	14 (17.5%)	9.7%	4.942	0.026
Cerebrovascular disease	12 (5.2%)	5 (3.3%)	7 (8.8%)	5.5%	3.232	0.072
Chronic pulmonary disease	20 (8.6%)	12 (7.8%)	8 (10.0%)	2.2%	0.311	0.577
qSOFA score	0 (0–1)	0 (0–1)	1 (0–1)	1	1.632	0.103
Systolic blood pressure ≤ 100 mmHg	15 (6.4%)	8 (5.2%)	7 (8.8%)	3.6%	1.081	0.298
Respiratory rate ≥ 22 breaths per min	102 (43.8%)	63 (41.2%)	39 (48.8%)	7.6%	1.224	0.269
Altered mentation	6 (2.6%)	2 (1.3%)	4 (5.0%)	3.7%	2.855	0.185
Disease severity classification at admission					18.644	< 0.001
Moderate	115 (49.4%)	89 (58.2%)	26 (32.5%)	–25.7%		
Severe	95 (40.8%)	56 (36.6%)	39 (48.8%)	12.2%		
Critical	23 (9.9%)	8 (5.2%)	15 (18.8%)	13.6%		
Laboratory findings						
White blood cell count ($\times 10^9$/L)	5.3 (4.3–7.2)	5.1 (4.1–6.2)	6.1 (4.9–9.1)	1.0	3.809	< 0.001
Lymphocyte count ($\times 10^9$/L)	1.0 (0.7–1.4)	1.1 (0.7–1.5)	0.9 (0.6–1.3)	–0.2	2.100	0.036
Alanine aminotransferase (U/L)	21 (14–39)	20 (14–36)	24 (16–43)	4	1.492	0.136
Creatinine (μmol/L)	70 (57–85)	68 (55–82)	76 (61–94)	8	2.223	0.026
Fasting plasma glucose (mmol/L)	5.8 (5.3–7.1)	5.5 (5.1–6.1)	7.5 (6.3–11.2)	2.0	8.527	< 0.001
HbA1c (%)[a]	6.4 (5.9–7.3)	6.0 (5.7–6.2)	7.2 (6.6–8.6)	1.2	9.563	< 0.001
HbA1c (mmol/mol) [a]	46 (41–56)	42 (39–44)	55 (49–70)	13	9.563	< 0.001
Interleukin-6 ≥ 13.26 pg/mL[b]	114/228 (50.0%)	69/148 (46.6%)	45/80 (56.3%)	9.7%	1.926	0.165
D-dimer ≥ 1 μg/mL[b]	114/229 (49.8%)	63/149 (42.3%)	51/80 (63.7%)	21.4%	9.596	0.002
In-hospital death	27 (11.6%)	9 (5.9%)	18 (22.5%)	16.6%	14.159	< 0.001

Data are expressed as median (interquartile range) or n (%) as appropriate. HbA1c: hemoglobin A1c; qSOFA: quick sequential organ failure assessment. [a] Analysed in 140 cases with HbA1c data. n=70 in the non-diabetes group and n=70 in the diabetes group. [b] Median value.

Table 2 Risk factors associated with in-hospital death in patients with COVID-19 by Cox regression analysis

Variables	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	*p* value
Demographic and clinical characteristics				
Age (years)	1.08 (1.04–1.12)	< 0.001	1.07 (1.02–1.10)	0.001
Sex−male	2.12 (0.95–4.72)	0.066	–	0.052
Diabetes	3.80 (1.71–8.47)	0.001	2.64 (1.14–6.11)	0.024
Diagnosed	4.03 (1.64–9.91)	0.002	–	–
Undiagnosed	1.89 (1.18–3.05)	0.009	–	–
Hypertension	1.45 (0.68–3.08)	0.339	–	–
Coronary artery disease	1.05 (0.32–3.49)	0.935	–	–
Cerebrovascular disease	2.68 (1.81–8.90)	0.108	–	–
Chronic pulmonary disease	2.54 (0.96–6.71)	0.060	–	0.134
qSOFA score	2.86 (1.68–4.87)	< 0.001	2.80 (1.58–4.97)	0.001
Laboratory findings at admission				
White blood cell count ($\times 10^9$/L)	1.19 (1.12–1.25)	< 0.001	–	–
Lymphocyte count ($\times 10^9$/L)	0.29 (0.11–0.77)	0.013	–	0.351
Alanine aminotransferase (U/L)	1.00 (0.99–1.01)	0.838	–	–
Creatinine (μmol/L)	1.00 (0.99–1.01)	0.112	–	–
Fasting plasma glucose (mmol/L)	1.14 (1.07–1.21)	< 0.001	–	–
HbA1c (%)	1.09 (0.81–1.45)	0.577	–	–
Interleukin-6 ≥ 13.26 pg/mL[a]	1.08 (0.49–2.36)	0.856	–	–
D-dimer ≥ 1 μg/mL[a]	5.77 (1.99–16.69)	0.001	3.28 (1.12–9.64)	0.030

HbA1c: hemoglobin A1c; HR: hazard ratio; qSOFA: quick sequential organ failure assessment. [a] Median value.

Figure titles and legends

Fig. 1 Flow diagram.

Fig. 2 Survival probability of inpatients with COVID-19.

Kaplan-Meier survival curves of patients with COVID-19 belonging to the overall diabetes (a), diagnosed diabetes (b), and undiagnosed diabetes (c) groups versus that of patients in the non-diabetes group. The blue and pink areas represent 95% CIs.

Supplementary Fig. 1 Survival probability of inpatients with COVID-19 who underwent HbA1c testing.

Kaplan-Meier survival curves of patients with COVID-19 belonging to the overall diabetes (a), diagnosed diabetes (b), and undiagnosed diabetes (c) groups versus that of patients without diabetes in a subgroup of participants who had their HbA1c tested at admission. The blue and pink areas represent 95% CIs.

Figures

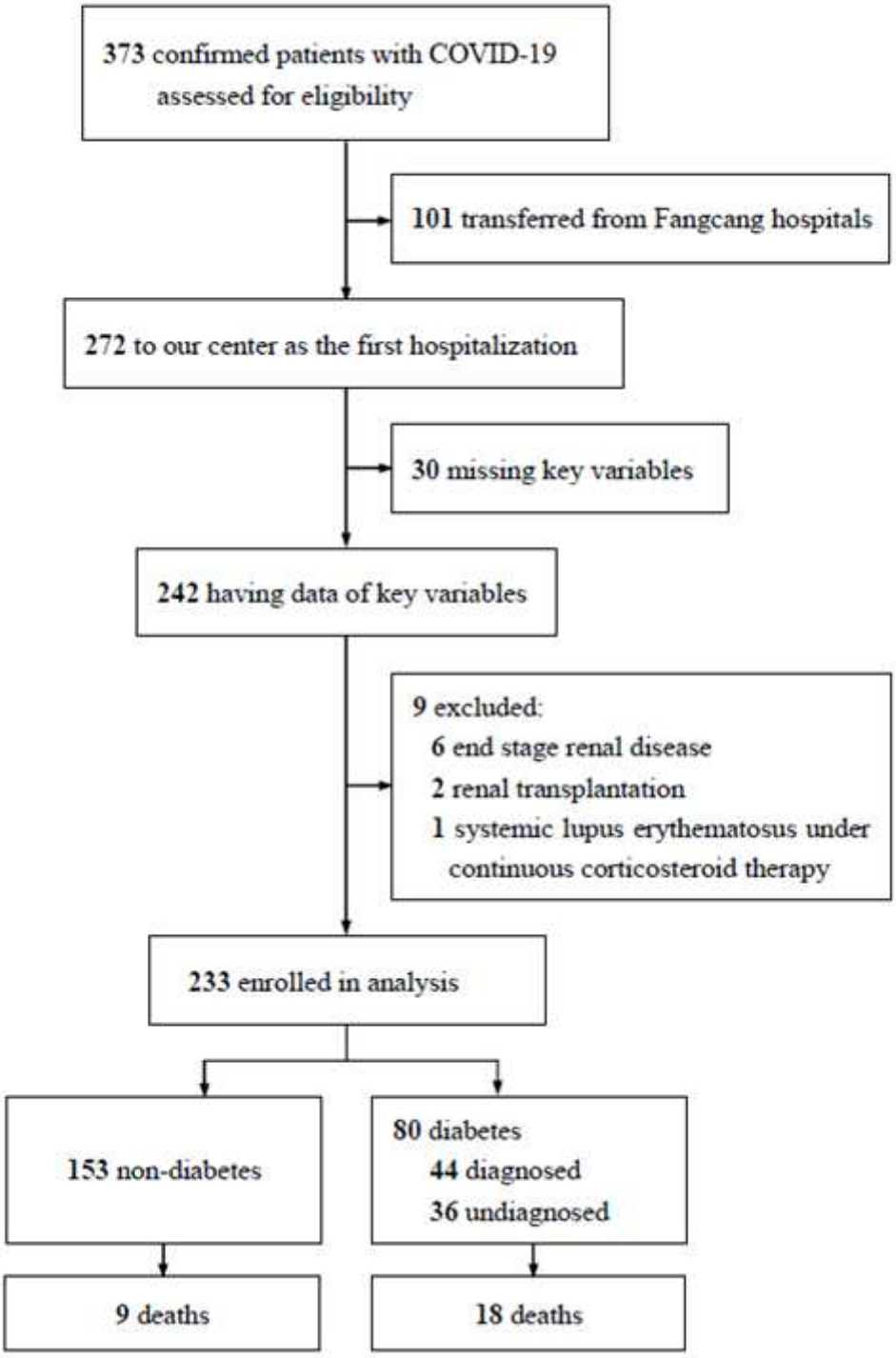

Figure 1

Flow diagram.

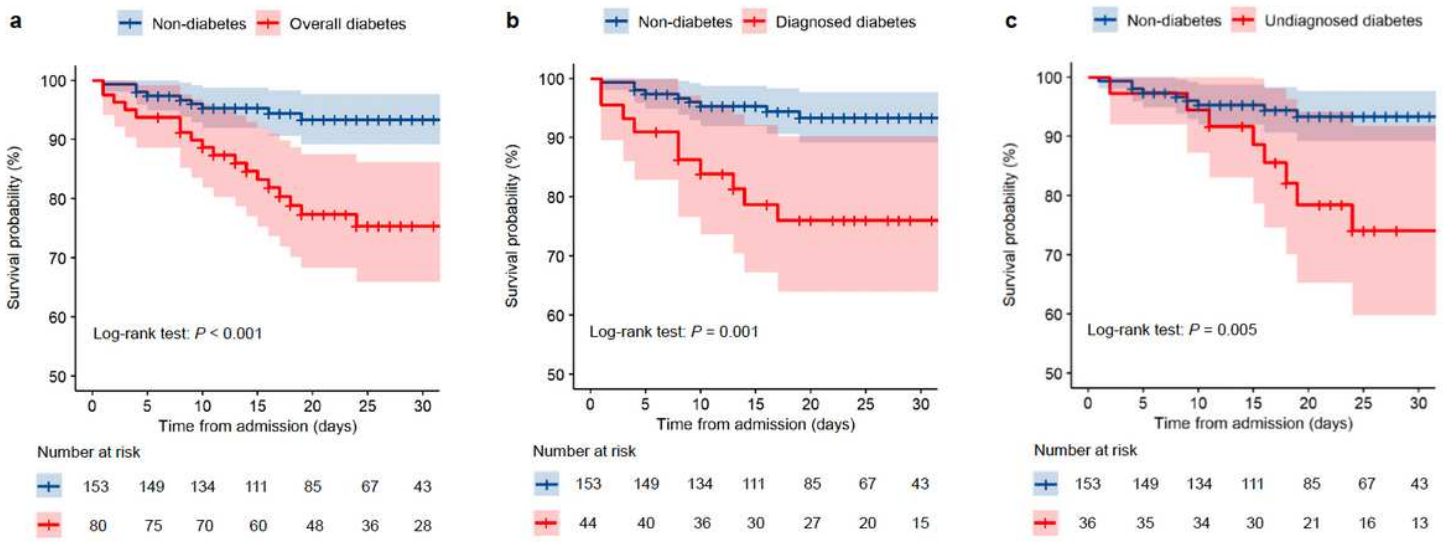

Figure 2

Survival probability of inpatients with COVID 19. Kaplan Meier survival curves of patients with COVID 19 belonging to the overall diabetes (a), diagnosed diabetes (b), and undiagnosed diabetes (c) groups versus that of patients in the non diabetes group. The blue and pink areas rep resent 95% CIs.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTablesandFigure.pdf