




## ORIGINAL ARTICLE

# Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19

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## Abstract

**Aim:** To evaluate the association between different degrees of hyperglycaemia and the risk of all-cause mortality among hospitalized patients with COVID-19.

**Materials and Methods:** In a retrospective study conducted from 22 January to 17 March 2020, 453 patients were admitted to Union Hospital in Wuhan, China, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection. Patients were classified into four categories: normal glucose, hyperglycaemia (fasting glucose 5.6–6.9 mmol/L and/or HbA1c 5.7%–6.4%), newly diagnosed diabetes (fasting glucose  $\geq 7$  mmol/L and/or HbA1c  $\geq 6.5\%$ ) and known diabetes. The major outcomes included in-hospital mortality, intensive care unit (ICU) admission and invasive mechanical ventilation (IMV).

**Results:** Patients with newly diagnosed diabetes constituted the highest percentage to be admitted to the ICU (11.7%) and require IMV (11.7%), followed by patients with known diabetes (4.1%; 9.2%) and patients with hyperglycaemia (6.2%; 4.7%), compared with patients with normal glucose (1.5%; 2.3%), respectively. The multivariable-adjusted hazard ratios of mortality among COVID-19 patients with normal glucose, hyperglycaemia, newly diagnosed diabetes and known diabetes were 1.00, 3.29 (95% confidence interval [CI] 0.65–16.6), 9.42 (95% CI 2.18–40.7) and 4.63 (95% CI 1.02–21.0), respectively.

**Conclusion:** We showed that COVID-19 patients with newly diagnosed diabetes had the highest risk of all-cause mortality compared with COVID-19 patients with known diabetes, hyperglycaemia and normal glucose. Patients with COVID-19 need to be kept under surveillance for blood glucose screening.

## KEYWORDS

diabetes complications, hypoglycaemia

## 1 | INTRODUCTION

The ongoing outbreak of COVID-19 is rapidly escalating worldwide. The new virus that caused this epidemic was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has now become a global catastrophe. As of 30 April 2020, ~3.1 million cases have been confirmed and there have been ~220 000 deaths caused by COVID-19 worldwide.<sup>1</sup> Recent data suggest that most people with COVID-19 have common co-morbidities including diabetes, cardiovascular disease and hypertension.<sup>2</sup>

Diabetes is one of the leading causes of morbidity, which results in a huge health and financial burden worldwide.<sup>3</sup> Diabetes is a primary risk factor for the development of severe pneumonia and sepsis because of virus infections and occurs in ~20% of patients with severe pneumonia.<sup>4,5</sup> Hyperglycaemia and a history of type 2 diabetes are independent predictors of mortality and morbidity in patients with SARS.<sup>6</sup> Diabetes is also identified as a major contributor to disease severity and mortality in Middle East respiratory syndrome (MERS-CoV).<sup>7</sup> Several studies have shown that COVID-19 is associated with hyperglycaemia, particularly in older people with type 2 diabetes.<sup>8</sup> Two recent studies found that 10.1% or 7.4% of COVID-19 patients reported a history of diabetes.<sup>9,10</sup> Two other studies suggest that the risk for death from COVID-19 is up to 50% higher in people with a history of diabetes than in those without.<sup>11,12</sup> However, no studies have evaluated the prospective association between hyperglycaemia assessed by laboratory measurements and the risk of mortality among patients with COVID-19. The first aim of the current study was to investigate the clinical characteristics, laboratory findings, treatments and major outcomes among hospitalized COVID-19 patients with different degrees of hyperglycaemia. The second aim was to assess the association between different degrees of hyperglycaemia and the risk of all-cause mortality among hospitalized patients with COVID-19.

## 2 | METHODS

### 2.1 | Study design and participants

This retrospective observational study included adult patients who were diagnosed with 2019 novel coronavirus pneumonia and hospitalized in Wuhan Union Hospital from 22 January to 17 March 2020. A diagnosis of COVID-19 illness was based on a positive SARS-CoV-2 laboratory result under World Health Organization (WHO) interim guidance.<sup>13</sup> The Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and Technology was designated by the government to undertake the treatment of severe COVID-19 patients. Up to 10 April 2020, 453 inpatients were included in the present analysis, of whom 39 died and 414 recovered. The study was approved by the ethics committee of the Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and Technology (ethical review no. 20200015). Written informed consent was waived owing to the rapid emergence of this infectious disease

and was replaced with oral consent. The study used anonymous clinical data for analysis.

### 2.2 | Data collection

Epidemiological data, clinical information, laboratory and radiological characteristics, chest computed tomography (CT) scan, treatment and outcome data of patients (recovery, death or transfer to other hospitals) were collected via a standardized electronic medical record data collection form. A well-trained team of doctors and researchers from the Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and Technology independently entered the data into a computer database and cross-checked it. Two researchers (S.T. and Z.C.) independently reviewed the clinical data of all laboratory-confirmed patients infected with SARS-CoV-2. If we were missing data for a particular patient then we contacted the clinician in charge of that patient's care to provide it. Because some patients were unable to co-operate with the medical history collection process upon their admission to hospital, we had to obtain their medical histories and other information by contacting close relatives and consulting medical records from previous hospital visits. Under government policy, some discharged patients were followed up and their details were recorded. Patients with incomplete information, especially those without clinical results, or those diagnosed with pneumonia by other known pathogens, were excluded.

Basic information (age, sex, smoking and shared medical history) and epidemiological exposure history were collected for each patient (addendum). A history of exposure was defined as exposure to a confirmed SARS-CoV-2 infection or to the Wuhan Huanan seafood market. Clinical manifestations (e.g. fever, fatigue, cough, myalgia, red eyes, dyspnea, headache, rhinorrhoea, chest pain, diarrhoea, nausea and vomiting, palpitations, loss of appetite), with the changes from onset to discharge, were recorded. Vital signs (heart rate, respiratory rate and blood pressure) were measured and recorded upon admission, and height and weight were self-reported. Within 3 days of admission to the hospital, laboratory results including standard blood count (absolute white blood cells and lymphocytes, haemoglobin concentration, platelet count, arterial blood gas analysis, supply, oxygen partial pressure), blood biochemistry (including kidney and liver, creatine kinase, fasting plasma glucose, HbA1c, electrolyte and lactate dehydrogenase), coagulation, procalcitonin, c-reactive protein (CRP), erythrocyte sedimentation rate, myocardial enzyme spectrum and normal bacteria, fungi and viruses, were input before the steroid therapy. Other data included medical imaging, treatment regimens (antiviral and antimicrobial agents, systemic corticosteroids, immunoglobulin G, respiratory support [such as nasal tubes, high-flow nasal intubation, non-invasive and invasive mechanical ventilation {IMV}]) and prognosis (discharge or death). Patients who recovered without any obvious symptoms and signs, and who had absorbed more lesions than before (as indicated by chest CT scan), and who also provided repeated negative results from SARS-Cov-2 virus nucleic acid tests, were discharged from the hospital.

## 2.3 | Classification of glucose abnormality

Patients were classified into four categories based on the first laboratory measurement and diabetes history after hospital admission: normal glucose, hyperglycaemia (fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7%-6.4%), newly diagnosed diabetes (fasting glucose  $\geq 7$  mmol/L and/or HbA1c  $\geq 6.5\%$ ) and known diabetes.

## 2.4 | Study outcomes

The main composite endpoints were IMV, admission to the intensive care unit (ICU), or death. The duration of follow-up for each patient (in person-days) was calculated from the first confirmed date of COVID-19 to the index date of discharge, death of inpatient, or transfer to another hospital. We also included other outcomes in the analyses. The definitions of SARS-CoV-2-associated acute respiratory distress syndrome (ARDS) and shock referred to the interim WHO guidance for SARS-CoV-2.<sup>13</sup> Acute cardiac injury was defined as elevated serum levels of cardiac biomarkers (such as CK-MB and hyper-sensitive cardiac troponin I) above the 99th percentile reference limit, or that new abnormalities were found during echocardiography.<sup>14</sup> Acute kidney injury was diagnosed according to KDIGO clinical practice guidelines.<sup>15</sup> In accordance with Chinese COVID-19 management guidelines (version 6.0), the severity of COVID-19 was divided into three levels: mild, severe and critical. Clotting disease was diagnosed if prothrombin time was prolonged for more than 3 seconds or if activation of partial thromboplastin time was prolonged for more than 5 seconds.<sup>16</sup> Hypoproteinaemia was defined as blood albumin less than 30 g/L.

## 2.5 | Statistical analysis

Differences in demographics, history of diseases, clinical symptoms, laboratory measurements, treatment and clinical outcomes among patients with different degrees of glucose status (normal glucose, hyperglycaemia, newly diagnosed diabetes and known diabetes) were assessed using Pearson's chi-square or Fisher's exact test for categorical variables and general linear model for continuous variables after adjustment for age and sex. Cox proportional hazards regression was used to estimate hazard ratios (HRs) for all-cause mortality among patients with different degrees of glucose status. Four models were used: model 1 adjusted for age and sex; model 2 adjusted for age, sex, smoking, systolic blood pressure and total cholesterol; model 3 adjusted for the variables in model 2 as well as IMV, admission to the ICU, and use of antihypertensive medications and lipid-lowering agents; model 4 adjusted for the variables in model 3 as well as the use of glucose-lowering drugs before hospital admission and during hospitalization, and of corticosteroid. We used the restricted cubic spline nested in time-dependent Cox models to test whether there was a dose-response or non-linear association of fasting glucose as a continuous variable with the all-cause mortality risk. All statistical

analyses were performed with SPSS statistics version 25.0 for Windows (IBM) and SAS for Windows version 9.3 (SAS Institute, Cary, NC, USA). Two-sided  $P < .05$  was considered statistically significant.

## 2.6 | Patient and public involvement

This was a retrospective study and no patients were directly involved in the study design, setting of research questions, or the outcome measures. No patients were asked to advise regarding the interpretation of or writing up of results.

## 3 | RESULTS

Until 17 March 2020, clinical data were collected from 453 patients with laboratory-confirmed SARS-Cov-2 infection. As of 10 April 2020, all hospitalized patients had outcomes, of whom, according to clinical classification, 114 patients were mild, 233 severe and 106 critical. General characteristics of the study population at baseline are given in Table 1. The median age of patients was 61 (interquartile range 49-68) years. Patients who had known diabetes, newly diagnosed diabetes and hyperglycaemia were slightly older, their baseline body mass index was higher, and they were more probably previous or current smokers and had more history of hypertension and stroke compared with those with normal glucose.

The laboratory variables among COVID-19 patients are presented in Table 2. Patients with newly diagnosed diabetes had the highest and patients with known diabetes had higher mean values of CRP, white blood cell count, erythrocyte sedimentation rate, fibrinogen, lactate dehydrogenase, blood urea nitrogen and fasting glucose than patients with either normal glucose or hyperglycaemia.

Table 3 shows the treatments and outcomes among COVID-19 patients with different degrees of glucose status. Patients with newly diagnosed diabetes were more probable to be admitted to the ICU (11.7%) and require IMV (11.7%), followed by patients with known diabetes (4.1%; 9.2%) and patients with hyperglycaemia (6.2%; 4.7%), compared with patients with normal glucose (1.5%; 2.3%), respectively. Patients with known diabetes and newly diagnosed diabetes had higher COVID-19-related complications including ARDS (3.1%-10.5% vs. 0.8%-3.1%), acute kidney injury (15.3%-17.0% vs. 1.5%-3.1%), shock (11.2%-23.4% vs. 2.3%-4.7%) and hypoalbuminemia (36.7%-39.4% vs. 10.8%-19.4%), as well as higher severe or critical types of COVID-19 (82.7%-89.4% vs. 61.4%-72.1%) compared with patients with normal glucose or hyperglycaemia. Patients with known diabetes and newly diagnosed diabetes were more probably using antihypertensive drugs, glucose-lowering medicines, lipid-lowering agents, were undergoing corticosteroid treatment, oxygen support and staying longer in hospital, compared with patients with normal glucose or slight hyperglycaemia at hospital admission.

During a mean follow-up period of 29.5 (range 1-70) days, 39 inpatients died. The results for the multivariate-adjusted Cox models for all-cause mortality in different glucose categories are shown in

**TABLE 1** Baseline characteristics according to different glucose categories among patients with COVID-19

	Normal glucose	Hyperglycaemia	Newly diagnosed diabetes	Known diabetes	P-values
No. of participants	132	129	94	98	
Age, years	51.9 (1.20)	57.5 (1.20)	62.2 (1.42)	65.3 (1.38)	<.001
Men, %	54 (40.9)	68 (52.7)	58 (61.7)	56 (57.1)	.011
Body mass index, kg/m <sup>2</sup> *	23.0 (0.36)	24.5 (0.34)	24.4 (0.45)	25.3 (0.41)	<.001
Systolic blood pressure, mmHg	130 (1.49)	132 (1.45)	131 (1.71)	135 (1.70)	.081
Diastolic blood pressure, mmHg	80.7 (1.04)	81.3 (1.01)	81.1 (1.19)	82.2 (1.18)	.825
Heart rate, times/minute	85.9 (3.69)	97.3 (3.59)	95.5 (4.25)	94.9 (4.23)	.136
Past or current smoking, %	11 (8.3)	21 (16.3)	19 (20.2)	19 (19.4)	.046
History of chronic diseases, %					
Diabetes	0 (0)	0 (0)	0 (0)	98 (100%)	-
Hypertension	25 (18.9)	33 (25.6)	39 (41.5)	53 (54.1)	<.001
Coronary heart disease	11 (8.3)	9 (7.0)	8 (8.5)	16 (16.3)	.092
Stroke	2 (1.5)	1 (0.8)	5 (5.3)	8 (8.2)	.007
Chronic pulmonary disease	4 (3.0)	10 (7.8)	4 (4.3)	7 (7.1)	.310
Chronic liver disease	1 (0.8)	3 (2.3)	6 (6.4)	2 (2.0)	.096
Chronic kidney disease	1 (0.8)	2 (1.6)	2 (2.1)	3 (3.1)	.649
Cancer	4 (3.0)	8 (6.2)	11 (11.8)	6 (6.2)	.070
Signs and symptoms, %					
Fever	95 (72.0)	106 (82.2)	77 (81.9)	72 (73.5)	.12
Cough	81 (61.4)	80 (62.0)	61 (64.9)	52 (53.1)	.36
Dyspnea	25 (18.9)	32 (24.8)	35 (37.2)	18 (18.4)	.006
Sputum production	30 (22.7)	37 (28.7)	26 (27.7)	18 (18.4)	.27
Haemoptysis	2 (1.5)	4 (3.1)	0 (0)	3 (3.1)	.29
Fatigue	41 (31.1)	62 (48.1)	47 (50.0)	45 (45.9)	.010
Headache	10 (7.6)	8 (6.2)	4 (4.3)	4 (4.1)	.63
Nausea or vomiting	6 (4.5)	8 (6.2)	9 (9.6)	9 (9.2)	.39
Diarrhoea	24 (18.2)	16 (12.4)	12 (12.8)	17 (17.3)	.48
Muscle soreness, unit	29 (22.0)	36 (27.9)	28 (29.8)	28 (28.6)	.53
Poor appetite	15 (11.4)	18 (14.0)	14 (14.9)	19 (19.4)	.40
Chest distress	23 (17.4)	27 (20.9)	30 (31.9)	20 (20.4)	.07
Palpitation	4 (3.0)	4 (3.1)	5 (5.3)	3 (3.1)	.79
Chest pain	3 (2.3)	2 (1.6)	0 (0)	1 (1.0)	.62
Rhinobyon	3 (2.3)	3 (2.3)	2 (2.1)	3 (3.1)	.98
Pharyngalgia	6 (4.5)	4 (3.1)	1 (1.1)	1 (1.0)	.33
Polypnea	19 (14.4)	26 (20.2)	19 (20.2)	20 (20.4)	.55
Arthralgia	1 (0.8)	0 (0)	0 (0)	1 (1.0)	.83
Dizziness	5 (3.8)	3 (2.3)	4 (4.3)	5 (5.1)	.73
Onset of symptom to, days					
Hospital admission	15.8 (1.12)	17.1 (1.09)	13.9 (1.27)	16.3 (1.28)	.29
Confirmation of COVID-19	9.1 (0.99)	10.3 (0.96)	9.9 (1.12)	10.4 (1.13)	.81
Exposure history, %					
Exposure to Huanan seafood market	0 (0)	1 (0.8)	1 (1.1)	0 (0)	.55
Exposure to infected cases	34 (25.8)	21 (16.3)	8 (8.5)	9 (9.2)	.004

Data are means (SE) and are adjusted for age and sex unless otherwise indicated as percentages.

\* Data were available for almost all participants.

Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; hyperglycaemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7%-6.4%; newly diagnosed diabetes, fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%; known diabetes, a history of diabetes.

**TABLE 2** Laboratory measurements according to different glucose categories among patients with COVID-19

	Normal glucose	Hyperglycaemia	Newly diagnosed diabetes	Known diabetes	P-values
No. of participants	132	129	94	98	
White blood cell count, $\times 10^9/L$	5.82 (0.25)	5.92 (0.24)	6.97 (0.28)	6.81 (0.28)	.003
Neutrophil count, $\times 10^9/L$	3.85 (1.10)	5.96 (1.07)	5.70 (1.26)	4.83 (1.25)	.53
Lymphocyte count, $\times 10^9/L$	1.41 (0.07)	1.45 (0.07)	0.94 (0.08)	1.36 (0.08)	<.001
Monocyte count, $\times 10^9/L$	0.45 (0.02)	0.43 (0.02)	0.35 (0.02)	0.45 (0.02)	.001
Platelet count, $\times 10^9/L$	214 (7.46)	226 (7.24)	214 (8.57)	215 (8.49)	.62
C-reactive protein, mg/L	18.3 (3.64)	24.4 (3.47)	52.2 (4.00)	36.6 (4.01)	<.001
Erythrocyte sedimentation rate, mm/h	34.9 (3.10)	47.1 (3.11)	58.9 (3.82)	51.0 (3.99)	<.001
Prothrombin time, s	13.4 (0.31)	13.0 (0.30)	14.1 (0.35)	13.3 (0.36)	.094
Activation of partial thromboplastin time, s	41.4 (2.55)	37.1 (2.46)	41.6 (2.88)	39.1 (2.96)	.56
D-dimer >0.5 mg/L, %	44 (42.7)	36 (33.6)	39 (55.7)	40 (53.3)	.011
Fibrinogen, g	3.57 (0.10)	3.90 (0.10)	4.17 (0.12)	4.18 (0.12)	<.001
Thrombin time, s	17.0 (0.67)	15.6 (0.64)	16.3 (0.75)	15.9 (0.77)	.49
Alanine aminotransferase, U/L	35.8 (3.30)	44.0 (3.19)	53.6 (3.77)	38.3 (3.75)	.003
Aspartate aminotransferase, U/L	32.2 (2.78)	34.7 (2.69)	50.7 (3.18)	32.7 (3.16)	<.001
Blood urea nitrogen, mmol/L	5.66 (0.42)	4.98 (0.40)	7.20 (0.47)	6.30 (0.47)	.004
Creatinine, $\mu\text{mol/L}$	84.8 (7.00)	70.4 (6.80)	74.4 (8.03)	72.8 (7.99)	.49
Lactate dehydrogenase	226 (12.9)	244 (12.5)	363 (14.6)	270 (14.5)	<.001
Total bilirubin, $\mu\text{mol/L}$	11.8 (0.87)	10.9 (0.84)	13.5 (0.99)	11.5 (0.98)	.22
Albumin, g/L	37.2 (1.67)	34.7 (1.61)	32.7 (1.91)	34.1 (1.90)	.37
Total cholesterol, mmol/L	4.21 (0.12)	4.62 (0.12)	4.18 (0.14)	4.22 (0.14)	.044
Triglycerides, mmol/L	1.39 (0.10)	1.58 (0.10)	1.66 (0.11)	1.72 (0.11)	.148
High-density lipoprotein cholesterol, mmol/L	1.13 (0.04)	1.03 (0.04)	1.05 (0.04)	0.99 (0.04)	.075
Low-density lipoprotein cholesterol, mmol/L	2.43 (0.10)	2.87 (0.10)	2.35 (0.11)	2.43 (0.11)	.001
Estimated glomerular filtration rate, mL/min/ 1.73m <sup>2</sup>	90.7 (12.5)	117 (12.1)	96.9 (14.3)	95.2 (14.2)	.44
Cystatin C, mg/L	0.83 (0.48)	1.10 (0.46)	2.77 (0.55)	1.04 (0.55)	.042
Fasting glucose, mmol/L	4.97 (0.18)	5.81 (0.18)	8.86 (0.21)	8.72 (0.21)	<.001
Procalcitonin, ng/ml	0.23 (0.16)	0.17 (0.14)	0.51 (0.18)	0.32 (0.17)	.49

Data are means (SE) and are adjusted for age and sex unless otherwise indicated as percentages.

Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; hyperglycaemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7%-6.4%; newly diagnosed diabetes, fasting glucose  $\geq 7$  mmol/L and/or HbA1c  $\geq 6.5\%$ ; known diabetes, a history of diabetes.

Table 4 and Figure 1. Relative to normal glucose, all-cause mortality increased in hyperglycaemia (HR 3.29; 95% confidence interval [CI] 0.65-16.6), newly diagnosed diabetes (HR 9.42; 95% CI 2.18-40.7) and known diabetes (HR 4.63; 95% CI 1.02-21.0) after adjusting for age, sex, smoking, systolic blood pressure and total cholesterol (model 2). After further adjustment for the use of antihypertensive drugs, lipid-lowering agents, admission to ICU and IMV (model 3), these associations did not change; however, the HR of mortality for known diabetes became higher than that for newly diagnosed diabetes after additional adjustments for the use of glucose-lowering drugs before hospital admission and during hospitalization, and of corticosteroid (model 4).

When fasting glucose was considered as a continuous variable by using restricted cubic splines, a graded positive association of fasting

glucose with all-cause mortality was observed among COVID-19 patients after excluding known diabetes (Figure 2).

To assess the potential hyperglycaemia exposed to COVID-19, we performed one sensitivity analysis among patients with newly diagnosed diabetes based upon the first laboratory measurement of fasting glucose and HbA1c after hospital admission. Multivariable-adjusted (model 2) HRs of mortality were 3.30 (95% CI 0.65-16.6) among patients with hyperglycaemia, 9.06 (95% CI 1.88-43.6) among patients with fasting glucose  $\geq 7$  mmol/L only but no measurement of HbA1c, 10.4 (95% CI 1.97-54.7) among patients with fasting glucose  $\geq 7$  mmol/L and HbA1c <6.5%, 9.23 (95% CI 1.87-45.5) among patients with fasting glucose  $\geq 7$  mmol/L and HbA1c  $\geq 6.5\%$ , and 4.62 (95% CI 1.02-20.9) among patients with known diabetes compared with patients with normal glucose (Table S1).

**TABLE 3** Treatments and outcomes according to different glucose categories among patients with COVID-19

	Normal glucose	Hyperglycaemia	Newly diagnosed diabetes	Known diabetes	P-values
No. of participants	132	129	94	98	
Treatments, %					
Antiviral therapy	114 (86.4)	117 (90.7)	84 (89.4)	80 (81.6)	.203
Antibiotic therapy	87 (65.9)	88 (68.2)	75 (79.8)	70 (71.4)	.132
Use of corticosteroid	26 (19.7)	38 (29.5)	44 (46.8)	36 (36.7)	<.001
Intravenous immunoglobulin	23 (17.4)	33 (25.6)	34 (36.2)	20 (20.4)	.009
Oxygen support, %	94 (71.2)	102 (79.1)	84 (89.4)	90 (91.8)	<.001
Nasal cannula	86 (65.2)	85 (65.9)	45 (47.9)	63 (64.3)	.023
Mask	2 (1.5)	4 (3.1)	11 (11.7)	10 (10.2)	.002
Non-invasive ventilation or high-flow nasal cannula	3 (2.3)	7 (5.4)	17 (18.1)	8 (8.2)	<.001
IMV	3 (2.3)	6 (4.7)	11 (11.7)	9 (9.2)	.018
Antihypertensive medicines	28 (21.2)	42 (32.6)	39 (41.5)	40 (40.8)	.003
Glucose-lowering medicines before hospital admission	0	0	0	60 (63.8)	-
Glucose-lowering medicines during hospital admission	1 (0.8)	4 (3.1)	23 (24.5)	68 (69.4)	<.001
Lipid-lowering medicine	6 (4.5)	12 (9.3)	10 (10.6)	15 (15.3)	.051
Illness severity, %					<.001
Non-severe	51 (38.6)	36 (27.9)	10 (10.6)	17 (17.3)	<.001
Severe or critical	81 (61.4)	93 (72.1)	84 (89.4)	81 (82.7)	<.001
Complications, %					
Acute respiratory distress syndrome	1 (0.8)	4 (3.1)	10 (10.6)	3 (3.1)	.001
Acute cardiac injury	27 (21.3)	26 (20.5)	23 (24.7)	32 (34.4)	.079
Acute kidney injury	2 (1.5)	4 (3.1)	16 (17.0)	15 (15.3)	<.001
Shock	3 (2.3)	6 (4.7)	22 (23.4)	11 (11.2)	.005
Hypoalbuminemia (albumin <30 g/L)	14 (10.8)	25 (19.4)	37 (39.4)	36 (36.7)	<.001
Coagulopathy	12 (10.1)	12 (10.1)	15 (17.0)	17 (19.5)	.070
Length of hospital stay, days	22.5 (1.19)	21.9 (1.16)	26.5 (1.37)	23.6 (1.37)	.046
ICU admission, %	2 (1.5)	8 (6.2)	11 (11.7)	4 (4.1)	.008
Prognosis, %					
Discharge, no	130 (98.5)	123 (95.3)	74 (78.7)	87 (88.8)	<.001
Death, no	2 (1.5)	6 (4.7)	20 (21.3)	11 (11.2)	<.001

Data are means (SE) and are adjusted for age and sex unless otherwise indicated as percentages.

Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; hyperglycaemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7%-6.4%; newly diagnosed diabetes, fasting glucose ≥7 mmol/L and/or HbA1c ≥6.5%; known diabetes, a history of diabetes.

## 4 | DISCUSSION

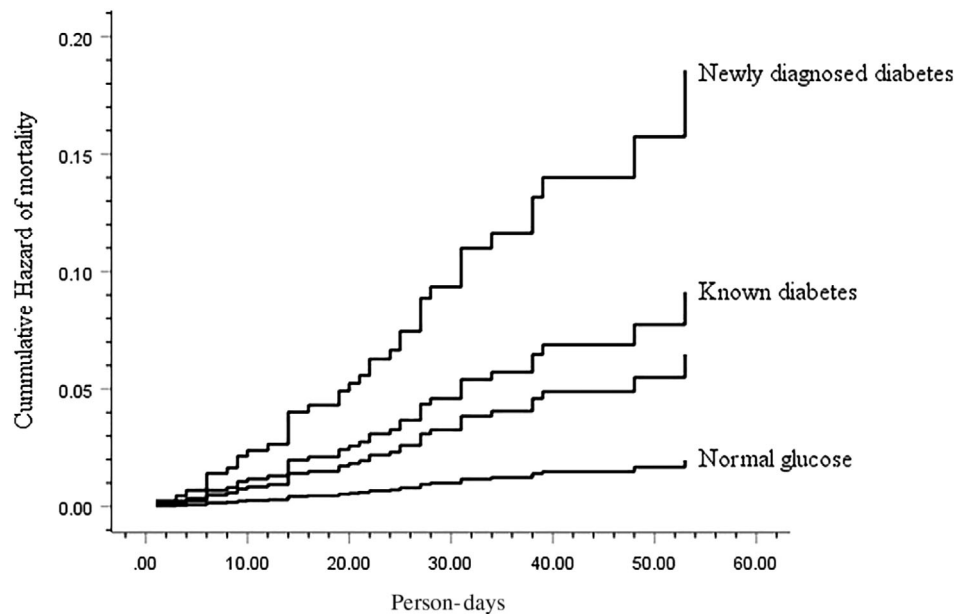
Our study found that newly diagnosed diabetes at first measurement upon hospital admission and a history of diabetes were both associated with an increased risk of all-cause mortality in hospitalized patients with COVID-19. Moreover, the current study is the first to show that COVID-19 patients with newly diagnosed diabetes based upon the first laboratory measurement after hospital admission had the highest risk of mortality compared with COVID-19 patients with known diabetes, hyperglycaemia and normal glucose, and that this association was independent of major cardiovascular risk factors.

Earlier studies have shown a link between a history of diabetes and COVID-19. Two studies in Wuhan indicated that 20% of 41 laboratory-confirmed COVID-19 patients (median age of 49 years)<sup>17</sup> and 10.1% of 138 laboratory-confirmed COVID-19 patients (median age of 56 years)<sup>9</sup> had a history of diabetes. According to the 2017 Chinese National Diabetes Survey, the prevalence of diabetes among people aged older than 20 years was 12.8% (6.0% of known diabetes and 6.8% of asymptomatic/newly diagnosed diabetes), and the prevalence of diabetes among people aged 60-69 years was 28.8% (14.9% of those with known diabetes and 13.9% of those with newly diagnosed diabetes).<sup>18</sup> The current study reported that at first

**TABLE 4** Hazard ratios of mortality according to different glucose categories among patients with COVID-19

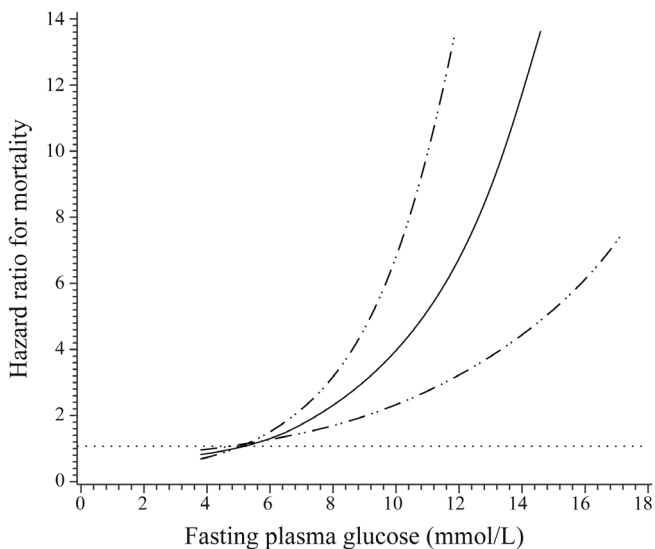
	Hazard ratios (95% confidence intervals)			
	Normal glucose	Hyperglycaemia	Newly diagnosed diabetes	Known diabetes
No. of participants	132	129	94	98
No. of cases	2	6	20	11
Person-days	3790	3769	2872	2916
Multivariable-adjusted model 1	1.00	2.84 (0.57-14.1)	9.43 (2.19-40.6)	4.57 (1.01-20.6)
Multivariable-adjusted model 2	1.00	3.29 (0.65-16.6)	9.42 (2.18-40.7)	4.63 (1.02-21.0)
Multivariable-adjusted model 3	1.00	3.27 (0.63-17.1)	7.21 (2.18-32.1)	6.06 (1.32-27.8)
Multivariable-adjusted model 4	1.00	2.64 (0.50-14.0)	5.63 (1.22-26.0)	8.76 (1.78-43.2)

Model 1 adjusted for age and sex; model 2 adjusted for age, sex, smoking, systolic blood pressure and total cholesterol; model 3 adjusted for the variables in model 2 and also for using antihypertensive drugs, using lipid-lowering agents, admission to ICU, and using IMV; model 4 adjusted for the variables in model 3 and also for using glucose-lowering drugs before admission as inpatients and during time as inpatients, and for using corticosteroid. Normal glucose, fasting glucose <5.6 mmol/L and HbA1c <5.7%; hyperglycaemia, fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7%-6.4%; newly diagnosed diabetes, fasting glucose  $\geq 7$  mmol/L and/or HbA1c  $\geq 6.5\%$ ; known diabetes, a history of diabetes.

**FIGURE 1** The cumulative hazard of mortality according to different glucose categories among patients with COVID-19. Adjusted for age, sex, smoking, systolic blood pressure and total cholesterol

measurement upon hospital admission, 21.6% of COVID-19 patients reported a history of diabetes, 20.8% were newly diagnosed with diabetes (fasting glucose  $\geq 7.0$  mmol/L and/or HbA1c  $\geq 6.5\%$ ), and 28.4% were diagnosed with hyperglycaemia (fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7%-6.4%), substantially higher compared with previous studies.<sup>9,17,18</sup> Several possible reasons for the higher prevalence of both known diabetes and newly diagnosed diabetes in the current study should be considered: (1) all of the study subjects were older with a median age of 61 years; (2) all the hospitalized patients had laboratory-confirmed COVID-19 and were experiencing a state of oxidative stress manifesting as hypoxia and inflammation, resulting in a significant rise in blood glucose. Our study also showed that patients with newly diagnosed diabetes and hyperglycaemia more often had fever, a cough and dyspnea, as well as higher levels of inflammatory indicators such as CRP, erythrocyte sedimentation rate and white blood cell count; and (3) COVID-19 infection reduces angiotensin-

converting enzyme 2 (ACE2) expression, which induced cellular damage, hyperinflammation and respiratory failure in our study population.<sup>19</sup> The expression of ACE2 on pancreatic beta-cells can lead to a direct effect on beta-cell function.<sup>20-22</sup> Although these findings have not been verified in humans, they suggest that diabetes might be a risk factor for a severe form of COVID-19 disease and that this infection could induce new-onset diabetes.<sup>20-22</sup> (4) Acute kidney injury and abnormal liver function were higher in the current study, especially in patients with newly diagnosed diabetes. Damage to the liver and kidneys, the key organs of glucose metabolism, can lead to a significant effect on blood glucose.<sup>23-25</sup> (5) The use of drugs, especially corticosteroids, can raise blood glucose. We found that the percentage of patients using corticosteroid was highest among those with newly diagnosed diabetes, followed by those with known diabetes and hyperglycaemia, compared with patients with normal blood glucose.



**FIGURE 2** Hazard ratios for all-cause mortality based on different levels of fasting plasma glucose among COVID-19 patients without known diabetes. Adjusted for age, sex, smoking, systolic blood pressure and total cholesterol

Population-based cohort studies have found that people with either a history of diabetes or asymptomatic diabetes had a higher risk of mortality than people with normal glucose.<sup>26</sup> However, very few studies have compared the mortality rate between COVID-19 patients with and without a history of diabetes or hyperglycaemia. One Chinese case-control study indicated that mortality rates were 35.4% and 20.3% among COVID-19 patients with and without a history of diabetes, respectively.<sup>27</sup> Another US study found that COVID-19 patients with a history of diabetes and/or uncontrolled hyperglycaemia had markedly higher mortality than patients without diabetes (28.8% vs. 6.2%).<sup>28</sup> However, no previous studies have assessed the association between different degrees of glucose status based on the American Diabetes Association's criteria and mortality, and no studies have controlled for potential confounding factors when assessing the above association. The current study showed that hospitalized COVID-19 patients with newly diagnosed diabetes at first measurement upon hospital admission were more probable to be admitted to the ICU and require IMV, had the highest prevalence of COVID-19-related complications including ARDS, acute kidney injury, shock and hypoalbuminemia, and also had the longest hospital stay, followed by patients with known diabetes and patients with hyperglycaemia, compared with patients with normal glucose. Moreover, we also showed that COVID-19 patients with newly diagnosed diabetes at first measurement upon hospital admission were at the highest risk of mortality compared with COVID-19 patients with known diabetes, hyperglycaemia and normal glucose, although we also found that COVID-19 patients with known diabetes had an increased risk of mortality compared with patients with normal glucose. These results were independent of major cardiovascular risk factors such as age, sex, smoking, blood pressure, blood total cholesterol, use of antihypertensive drugs, use of lipid-lowering agents, admission to ICU and

IMV. However, the relative risk of mortality among patients with known diabetes was higher in those with newly diagnosed diabetes after adjustment for the use of glucose-lowering drugs before hospital admission and during hospitalization, and the use of corticosteroid. Thus, it can be speculated that COVID-19 patients with known diabetes using glucose-lowering drugs to control blood sugar might benefit from a protective effect on the risk of death.

Because those COVID-19 patients with newly diagnosed diabetes after hospital admission could include patients with a significant rise in blood glucose as a result of stress manifesting as hypoxia and inflammation, as well as patients with asymptomatic diabetes, we also compared the relative risk of mortality among patients with newly diagnosed hyperglycaemia up to diabetes (fasting glucose  $\geq 7.0$  mmol/L and HbA1c  $< 6.5\%$ ) with patients with asymptomatic diabetes (fasting glucose  $\geq 7.0$  mmol/L and HbA1c  $\geq 6.5\%$ ). Patients with hyperglycaemia up to diabetes and patients with asymptomatic diabetes contributed equally to the risk of all-cause mortality, and both had a higher risk of mortality than patients with known diabetes compared with patients with normal glucose (Table S1). These results suggest that the risk of disease severity and poor prognosis of COVID-19 (including mortality) significantly increase with newly diagnosed diabetes after hospital admission. Thus, COVID-19 patients need to be under surveillance for blood glucose screening, and for those patients with newly diagnosed diabetes with COVID-19-related complications, more attention should be paid to combination therapy.

Some mechanisms indicate that newly diagnosed diabetes and/or known diabetes might play a role in COVID-19 infection and poor prognosis. Hyperglycaemia and a history of diabetes are independent predictors of mortality and morbidity in patients with SARS.<sup>6</sup> It could be that these patients have a state of metabolic inflammation that predisposes them to an enhanced release of cytokines. For COVID-19, a cytokine storm which showed greatly elevated levels of inflammatory cytokines has been implicated in multi-organ failure in patients with severe disease.<sup>29</sup> Metabolic inflammation caused by hyperglycaemia can also damage the immune system, reducing the body's ability to cope with infection, impairing the healing process and prolonging the recovery time. An animal model shows that the complication of type 2 diabetes causes an immune disorder and enhances disease severity following MERS-CoV infection.<sup>30</sup> On the other hand, ACE2 has been confirmed as the receptor for the coronavirus spike protein. ACE2 has protective effects primarily regarding inflammation. COVID-19 infection reduces ACE2 expression, which induces cellular damage, hyperinflammation and respiratory failure.<sup>19</sup> Acute hyperglycaemia has been shown to upregulate ACE2 expression on cells that might facilitate viral cell entry, while chronic hyperglycaemia is known to downregulate ACE2 expression, making cells vulnerable to the inflammatory and damaging effects of the virus.<sup>12</sup> This may be one reason why patients with newly diagnosed diabetes have a worse prognosis than those with known diabetes.

This is the first retrospective study to assess the risk of mortality among patients with laboratory-confirmed COVID-19 by examining different degrees of hyperglycaemic status by laboratory measurements. The comparatively rich clinical data and numerous events also



strengthen the results. However, there are some limitations to this study. First, although our analyses adjusted for some confounding factors, unmeasured factors, such as body mass index and beta-cell auto-antibodies, could not be evaluated because there was insufficient maintenance in the early stages of the outbreak of the epidemic, and no height or weight measurements were obtained for those patients who were severely ill or who died during hospitalization. Second, not all patients had HbA1c tests, which may have some impact upon the accuracy of our blood glucose groupings. Third, using fasting glucose  $\geq 7.0$  mmol/L and HbA1c  $\geq 6.5\%$  as cut-off points for newly diagnosed diabetes could produce potential misclassification bias because a significant rise in blood glucose for stress manifesting as hypoxia and inflammation was found among patients after COVID-19. We used this definition to focus more attention on clinical screening and treatment among COVID-19 patients with newly diagnosed diabetes at hospital admission.

In conclusion, the current study found that hospitalized COVID-19 patients with newly diagnosed diabetes and known diabetes had an increased risk of all-cause mortality. COVID-19 patients with newly diagnosed diabetes had the highest risk of all-cause mortality compared with COVID-19 patients with known diabetes, hyperglycaemia and normal glucose. Our study suggests that patients with COVID-19 need to be kept under surveillance for blood glucose screening, and for those patients with newly diagnosed diabetes with COVID-19-related complications, more attention should be paid to combination therapy.

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#### CONFLICT OF INTEREST

All the authors declare no conflict of interest.

#### AUTHOR CONTRIBUTIONS

H.L., S.T. and T.C. drafted the manuscript. J.Z., H.L., T.Z., L.C. and J.Z. performed the literature research. S.T., Z.C., N.S., X.Z., K.Q. and H.L. collected the epidemiological and clinical data. T.C., H.L. and N.S. contributed to the statistical analysis. T.C. created the tables. J.Z. and L.C. conceived and supervised the overall study. All the authors reviewed and approved the final version of the manuscript. H.L., S.T. and T.C. contributed equally to this study and should be regarded as co-first authors.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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