


ORIGINAL ARTICLE

The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: A single-centre, retrospective, observational study in Wuhan

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Abstract

Aim: To explore whether coronavirus disease 2019 (COVID-19) patients with diabetes and secondary hyperglycaemia have different clinical characteristics and prognoses than those without significantly abnormal glucose metabolism.

Materials and methods: We retrospectively analysed 166 COVID-19 patients at Tongji Hospital (Wuhan) from 8 February to 21 March 2020. Clinical characteristics and outcomes (as of 4 April 2020) were compared among control (group 1), secondary hyperglycaemia (group 2: no diabetes history, fasting plasma glucose levels of ≥ 7.0 mmol/L once and HbA1c values $< 6.5\%$) and patients with diabetes (group 3).

Results: Compared with group 1, groups 2 and 3 had higher rates of leukocytosis, neutrophilia, lymphocytopenia, eosinopenia and levels of hypersensitive C-reactive protein, ferritin and d-dimer ($P < .05$ for all). Group 2 patients had higher levels of lactate dehydrogenase, prevalence of liver dysfunction and increased interleukin-8 (IL-8) than those in group 1, and a higher prevalence of increased IL-8 was found in group 2 than in group 3 ($P < .05$ for all). The proportions of critical patients in groups 2 and 3 were significantly higher compared with group 1 (38.1%, 32.8% vs. 9.5%, $P < .05$ for both). Groups 2 and 3 had significantly longer hospital stays than group 1, which was nearly 1 week longer. The composite outcomes risks were 5.47 (1.56-19.82) and 2.61 (0.86-7.88) times greater in groups 2 and 3 than in group 1.

Conclusions: Hyperglycaemia in both diabetes and secondary hyperglycaemia patients with COVID-19 may indicate poor prognoses. There were differences between patients with secondary hyperglycaemia and those with diabetes. We recommend that clinicians pay more attention to the blood glucose status of COVID-19 patients, even those not diagnosed with diabetes before admission.

KEYWORDS

cohort study, type 2 diabetes

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is sweeping across the globe, resulting in >3 059 642 confirmed cases and 211 028 deaths worldwide as of 30 April 2020. The mortality rates reported for COVID-19 patients are considerable yet also appear to be wide-ranging (1.4%-15%).¹⁻⁵ These large differences in patient mortality may be attributed to pre-existing characteristics such as age, co-morbidities and disease severity.

Some studies have shown that severe COVID-19 patients have a higher incidence of diabetes than non-severe COVID-19 patients (13.8%-40.0% vs. 3.5%-11.0%).^{1,3,4,6,7} Moreover, the proportion of patients with diabetes was higher among the deceased than those who survived (22%-31% vs. 10%-14%).^{2,8} Similar phenomena have been observed in the two other kinds of coronavirus disease, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Both mortality and severe disease manifestations in SARS and MERS are related to pre-existing diabetes.^{9,10} SARS was also found to cause secondary hyperglycaemia in patients who had no history of diabetes and had not used any glucocorticoids during the course of the disease.¹¹

To date, to our knowledge, there have been few studies comparing clinical features and prognoses between diabetic and non-diabetic COVID-19 patients. Guo et al found that diabetes was associated with a worse prognosis in COVID-19 patients.¹² In the case of COVID-19, whether this susceptibility to disease severity is particularly high or only reflects the greater risk posed by diabetes, is still uncertain.¹³ Furthermore, the impact of secondary hyperglycaemia on the outcomes of patients with COVID-19 is also unknown. The aim of this single-centre retrospective study was to explore whether COVID-19 patients with diabetes and secondary hyperglycaemia have different clinical characteristics and prognoses than those without significantly abnormal glucose metabolism. As COVID-19 is now a global pandemic, we believe that this information will be useful for physicians treating the growing number of COVID-19 patients who have diabetes or underlying hyperglycaemia.

2 | METHODS

2.1 | Study design and participants

This retrospective study was an exploratory comparison of COVID-19 patients with diabetes, those with secondary hyperglycaemia and control patients. All patients were hospitalized in three wards of Tongji Hospital in the Zhongfa district of Wuhan from 8 February to 21 March 2020. This study was approved by the institutional ethics board of Peking University First Hospital (No. 2020-090).

From the end of January, adult COVID-19 patients were admitted to hospitals in Wuhan under the supervision of the Wuhan Municipal Government Command Center. All COVID-19 patients sent to our centre and enrolled in this study were diagnosed according to the guidelines for COVID-19 issued by the Chinese National Health Committee (version 7). The guidelines categorized adult patients as having mild, moderate, severe or critical cases.¹⁴ Only patients with moderate, severe and critical cases were sent to our centre.

All laboratory tests were based on the patients' clinical needs. Fasting plasma glucose (FPG) was tested the morning after admission (before the commencement of glucocorticoid therapy). Patients with FBG levels of ≥ 7.0 mmol/L were re-examined and their HbA1c levels were determined during the next few days. The patients were divided into three groups based on their diabetes history and FPG and HbA1c levels. Group 1 ($n = 84$) was composed of patients without a history of diabetes whose FPG levels were < 7.0 mmol/L; this group was defined as the control group. Group 2 ($n = 21$) was composed of patients with FPG levels of ≥ 7.0 mmol/L once and HbA1c levels of $< 6.5\%$; this group was defined as the secondary hyperglycaemia group. Group 3 ($n = 61$) was composed of patients with a history of diabetes, FBG levels of ≥ 7.0 mmol/L twice or HbA1c levels of $\geq 6.5\%$; this group was defined as the diabetes group.¹⁵ Considering that, compared with FPG, the short-term stress response caused by the viral infection before admission had less impact on HbA1c, the HbA1c levels were prioritized over the FPG levels in the grouping criteria for patients without a diabetes history to avoid overestimating the incidence of diabetes.

2.2 | Variables

The data were obtained from the electronic medical records system (Tongji Hospital Cloud Hospital Information System). Information regarding epidemiology, demographics, clinical symptoms and signs, medical history of concomitant diseases, laboratory inspections, chest computed tomography (CT) scans, treatment(s) during hospitalization and clinical outcomes was collected for each patient and compared among the three groups.

Medical laboratory results included a complete blood count, serum biochemical test (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatine, estimated glomerular filtration rate [eGFR; based on the Chronic Kidney Disease Epidemiology Collaboration equation], creatine kinase [CK] and lactate dehydrogenase [LDH]), plasma glucose, coagulation profile, myocardial enzyme test (cardiac troponin I, CK myocardial band [CK-MB], myoglobin and n-terminal pro-brain natriuretic peptide [NT-proBNP]), inflammatory markers [erythrocyte sedimentation rate [ESR], hypersensitive C-reactive protein [sCRP], ferritin and procalcitonin [PCT]) and cytokines (interleukin- 1β , interleukin-2 receptor, interleukin [IL]-6, -8 and -10, and tumour necrosis factor- α). HbA1c was measured by high performance liquid chromatography (Arkray, HA-8180). Nasopharyngeal swabs were tested for the RNA of SARS coronavirus-2 (SARS-CoV-2) using real-time RT-PCR assay by the hospital viral laboratory.

2.3 | Outcomes

We described the epidemiology (exposure to confirmed patients), demographics, clinical symptoms and signs on admission, reported medical history of concomitant diseases, laboratory tests, CT scans (first CT scan of patients before admission), clinical classification,

treatments during hospitalization (including medication and oxygen therapy) and clinical outcomes (discharge, hospitalization and death). Composite outcomes were defined as admission to an intensive care unit (ICU), the use of mechanical ventilation (both invasive and non-invasive types) or death. All of the above-mentioned data were compared among the three groups. Fitness for discharge was based on improved respiratory symptoms, no fever for at least 3 consecutive days, improved chest radiographic evidence, and negative results for

SARS-CoV-2 RNA in sputum, nasopharyngeal swabs and other respiratory specimens twice (interval >24 hours).¹⁴

2.4 | Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables are presented as the

TABLE 1 Demographic and baseline characteristics of coronavirus disease 2019 patients

	All patients (n = 166)	Group 1 (n = 84)	Group 2 (n = 21)	Group 3 (n = 61)	P value
Characteristics					
Age, years	62.7 ± 14.2	59.4 ± 16.0	67.6 ± 10.2 ^a	65.6 ± 11.4 ^a	.007
Male, n (%)	85 (51.2)	41 (48.8)	11 (52.4)	33 (54.1)	.983
BMI, kg/m ²	24.2 ± 3.6	23.6 ± 3.3	24.2 ± 3.9	25.1 ± 3.7	.062
Overweight and obesity, n (%)	91 (54.8)	43 (51.2)	11 (52.4)	37 (60.7)	.371
Exposure to patients ^b , n (%)	71 (42.8)	38 (45.2)	5 (23.8)	28 (45.9)	.171
Duration from illness onset to diagnosis, days	7.0 (3.0-11.0)	7.0 (4.0-11.0)	6.5 (2.0-10.3)	7.0 (3.0-9.5)	.306
Current smoking, n (%)	31 (18.7)	12 (14.3)	7 (33.3)	12 (19.7)	.130
Co-morbidities, n (%)					
Hypertension	76 (45.8)	30 (35.7)	11 (52.4)	35 (57.4) ^a	.029
Cardiovascular disease	30 (18.1)	10 (11.9)	4 (19.0)	16 (26.2)	.086
Chronic pulmonary disease	19 (11.4)	9 (10.7)	1 (4.8)	9 (14.7)	.443
Chronic kidney disease	9 (5.4)	6 (7.1)	0	3 (4.9)	.640
Cerebrovascular disease	12 (7.2)	3 (3.6)	3 (14.3)	6 (9.8)	.124
Thyroid disease	3 (1.8)	2 (2.4)	0	1 (1.6)	1.000
Digestive system disease	5 (3.0)	2 (2.4)	1 (4.8)	2 (3.3)	.824
Malignancy	3 (1.8)	0	0	3 (4.9)	.091
Symptoms, n (%)					
Fever	139 (83.7)	70 (83.3)	16 (76.2)	53 (86.9)	.514
Peak temperature, °C	38.6 ± 0.7	38.6 ± 0.6	38.5 ± 0.9	38.5 ± 0.8	.782
Cough	136 (81.9)	71 (84.5)	15 (71.4)	50 (82.0)	.378
Expectoration	90 (54.2)	45 (53.6)	8 (38.4)	37 (60.7)	.199
Dyspnea	115 (69.3)	55 (65.5)	16 (76.4)	44 (72.1)	.529
Hemoptysis	16 (9.6)	5 (6.0)	1 (4.8)	10 (16.4)	.079
Chest pain	25 (15.1)	10 (11.9)	4 (19.0)	11 (18.0)	.513
Sore throat	30 (18.1)	15 (17.9)	6 (28.6)	9 (14.8)	.364
Diarrhoea	77 (46.4)	37 (44.0)	10 (47.6)	30 (49.2)	.823
Nausea	47 (28.3)	21 (25.0)	6 (28.6)	20 (32.8)	.590
Vomiting	26 (15.7)	12 (14.3)	5 (23.8)	9 (14.8)	.545
Anorexia	75 (45.2)	38 (45.2)	10 (47.6)	27 (44.3)	.965
Stomach ache	16 (9.6)	9 (10.7)	2 (9.5)	5 (8.2)	.879
Headache	53 (31.9)	27 (32.1)	9 (42.9)	17 (27.9)	.445
Muscle pain	63 (38.0)	31 (36.9)	7 (33.3)	25 (41.0)	.792
Fatigue	99 (59.6)	49 (58.3)	15 (71.4)	35 (57.4)	.496
Palpitation	40 (24.1)	20 (23.8)	6 (28.6)	14 (23.0)	.870
Night sweat	32 (19.3)	13 (15.5)	2 (9.5)	17 (27.9)	.084
Shock on admission	2 (1.2)	0	1 (4.8)	1 (1.6)	.109

(Continues)

TABLE 1 (Continued)

	All patients (n = 166)	Group 1 (n = 84)	Group 2 (n = 21)	Group 3 (n = 61)	P value
Admission vital signs					
Heart rate, beats per minute	96.7 ± 18.0	95.5 ± 16.0	98.8 ± 16.0	97.5 ± 21.2	.671
Mean blood pressure, mmHg	107.1 ± 16.5	106.2 ± 15.7	112.4 ± 15.6	106.4 ± 17.6	.283
Respiratory rate, /min	22.0 (20.0-25.0)	22.0 (20.0-24.0)	24.0 (21.0-29.0)	22.0 (20.0-26.0)	.183
Temperature, °C	36.6 (36.2-37.1)	36.7 (36.4-37.4)	36.3 (36.1-37.0) ^a	36.5 (36.2-36.9) ^a	.012
Pulse oximeter oxygen saturation, %	94.0 (88.0-97.0)	94.0 (90.0-97.8)	93.0 (73.5-97.0)	95.0 (86.0-97.0)	.117
≤93%, n (%)	75 (45.2)	35 (41.7)	11 (52.4)	29 (47.5)	.608

Data are n (%), mean ± SD and median (interquartile range). The continuous variables with normal or non-normal distributions were compared among the three groups using ANOVA and independent t tests, or Kruskal–Wallis and Mann–Whitney tests. The χ^2 or Fisher exact test was used to compare categorical variables among the three groups. Group 1: control group; group 2: secondary hyperglycaemia group; group 3: diabetes group. Body mass index (BMI) was calculated as the weight, divided by height squared (kg/m^2). Overweight and obesity were defined as $\text{BMI} \geq 23 \text{ kg}/\text{m}^2$. The P value indicates differences among groups 1, 2 and 3.

^aP < .05 relative to group 1.

^bPatients who have confirmed severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection or are highly suspected of being infected.

mean (standard deviation) and skewed data are presented as the median (interquartile range). The data in different groups were compared with the ANOVA or independent t test for normally distributed variables or the Kruskal–Wallis test and Mann–Whitney test for non-normally distributed variables. Categorical variables are presented as the frequency (percentage) and were compared by χ^2 test or Fisher's exact test. Logistic regression analysis was performed to assess the composite outcomes of the three groups after adjusting for confounders (age, sex, body mass index [BMI], medical histories of hypertension, cardiovascular disease and malignancy). A P value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Basic characteristics and vital signs on admission

The basic characteristics of all 166 patients are shown in Table 1. Patients in groups 2 and 3 were significantly older than those in group 1 (67.6 ± 10.2 and 65.6 ± 11.4 vs. 59.4 ± 16.0 years, $P = .005$ and $P = .007$). The sex distributions and proportions of overweight and obese individuals ($\text{BMI} \geq 23 \text{ kg}/\text{m}^2$) were comparable among the three groups. The BMI values of the three groups appeared to be different ($P = .062$) and showed a gradual increasing trend among the groups. The proportion of hypertensive patients in group 3 was significantly higher than that in group 1 (57.4% vs. 35.7%, $P = .01$) and no significant difference was found in other co-morbidities among the three groups. In all hypertensive patients, the proportion of Renin-Angiotensin-Aldosterone system inhibitors was 32.9% (25/76), and the percentage of calcium antagonists, β -receptor blockers and α -receptor blockers was 60.5%, 28.9% and 1.3%, respectively. There was no significant difference in any kind of antihypertensive drug among the three groups (all $P > .05$).

There were no significant differences in all symptoms, signs and most of the vital signs among the three groups. Lower levels of temperature on admission were found in groups 2 and 3 compared with those in group 1 (36.3 [36.1-37.0] and 36.5 [36.2-36.9] vs. 36.7 [36.4-37.4]°C, $P = .033$ and $P = 0.01$).

3.2 | Laboratory variables

Several laboratory test results differed among the three groups (Table 2). With regard to the complete blood count, the levels of leukocytes and neutrophils in groups 2 and 3 were both significantly higher than those in group 1 ($P < .05$ for both). The ratios of neutrophilia in groups 2 and 3 were also higher than those in group 1 (52.4% vs. 10.7%, $P < .001$; and 31.1% vs. 10.7%, $P = .002$, respectively). The levels of lymphocytes were significantly lower in groups 2 ($0.7 [0.6-1.3]$ vs. $1.1 [0.8-1.6] \times 10^9/\text{L}$, $P = .016$) and 3 ($0.9 [0.5-1.3]$ vs. $1.1 [0.8-1.6] \times 10^9/\text{L}$, $P = .017$) than in group 1. The level of eosinophils in group 1 was significantly higher than those in groups 2 ($0.04 [0.01-0.98]$ vs. $0 [0-0.06] \times 10^9/\text{L}$, $P = .017$) and 3 ($0.04 [0.01-0.98]$ vs. $0.01 [0-0.07] \times 10^9/\text{L}$, $P = .029$). In addition, the reductions in eosinophils were significantly greater in groups 2 (66.7% vs. 38.1%, $P = .018$) and 3 (59.0% vs. 38.1%, $P = .013$) than in group 1. The above indicators were comparable for patients in groups 2 and 3.

Compared with groups 1 and 3, group 2 patients had the highest prevalence (up to 50%) of elevated ALT levels ($P = .007$ and $P = .048$), and significantly higher levels of AST ($P = .008$ and $P = .037$). The serum creatinine level ($75.0 [63.5-98.0]$ vs. $69.0 [56.3-86.0] \mu\text{mol}/\text{L}$, $P = .039$) was significantly higher, and the eGFR level (72.1 ± 23.2 vs. $83.5 \pm 25.3 \text{ mL}/\text{min}/1.73 \text{ m}^2$, $P = .006$) was significantly lower in group 3 than in group 1 patients. There were more patients with eGFR levels of within $30-60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ in group 3 compared with groups 1 (31.1% vs. 14.3%, $P = .014$) and 2 (31.1% vs. 9.5%, $P = .05$). Hypoproteinaemia was more common in groups 2 and 3 compared with group 1 ($P < .05$ for both).

TABLE 2 Laboratory tests and radiographic findings of patients with coronavirus disease 2019 on admission to the hospital

	Normal ranges	All patients (n = 166)	Group 1 (n = 84)	Group 2 (n = 21)	Group 3 (n = 61)	P value
Fasting plasma glucose, mmol/L	4.11-6.05	6.2 (5.2-8.0)	5.3 (4.9-5.8)	7.7 (7.2-8.8) ^a	8.5 (6.7-12.1) ^a	<.001
HbA1c, % ^b	4-6	6.4 (6.0-7.2)	6.0 (5.7-6.2)	6.2 (6.0-6.4)	7.1 (6.6-8.4) ^{a,c}	<.001
Leucocytes, ×10 ⁹ /L	3.5-9.5	5.6 (4.4-7.8)	5.1 (4.1-6.2)	7.8 (5.0-13.2) ^a	6.5 (4.9-8.7) ^a	<.001
Decreased, n (%)		20 (12.0)	14 (16.7)	1 (4.8)	5 (8.2)	.166
Increased, n (%)		27 (16.3)	8 (9.5)	8 (38.1) ^a	11 (18.0)	.006
Neutrophils, ×10 ⁹ /L	1.8-6.3	4.0 (2.7-6.0)	3.3 (2.3-4.4)	6.9 (3.1-11.9) ^a	4.6 (3.2-6.9) ^a	<.001
Decreased, n (%)		10 (6.0)	7 (8.3)	1 (4.8)	2 (3.3)	.480
Increased, n (%)		39 (23.5)	9 (10.7)	11 (52.4) ^a	19 (31.1) ^a	<.001
Lymphocytes, ×10 ⁹ /L	1.1-3.2	1.0 (0.7-1.5)	1.1 (0.8-1.6)	0.7 (0.6-1.3) ^a	0.9 (0.5-1.3) ^a	.012
Decreased, n (%)		92 (55.4)	41 (48.8)	15 (71.4)	36 (59.0)	.136
Eosinophil, ×10 ⁹ /L	0.02-0.52	0.03 (0-0.08)	0.04 (0.01-0.98)	0 (0-0.06) ^a	0.01 (0-0.07) ^a	.015
Decreased, n (%)		82 (49.4)	32 (38.1)	14 (66.7) ^a	36 (59.0) ^a	.011
Haemoglobin, g/L	130-175	125.5 ± 19.0	124.5 ± 16.3	134.2 ± 16.0	123.9 ± 22.6	.076
Decreased, n (%)		103 (62.0)	53 (63.1)	9 (42.9)	41 (67.2)	.134
Platelets, ×10 ⁹ /L	125-350	232.7 ± 92.1	232.5 ± 84.7	201.8 ± 108.6	243.8 ± 94.8	.197
Decreased, n (%)		16 (9.6)	7 (8.3)	5 (23.8)	4 (6.6)	.059
Increased, n (%)		19 (11.4)	8 (9.5)	2 (9.5)	9 (14.8)	.594
Alanine aminotransferase, U/L	≤41	21.5 (14.0-40.0)	20.0 (13.0-29.8)	38.0 (15.5-50.0)	24.0 (15.0-41.0)	.077
Increased, n (%)		39 (23.5)	14 (16.7)	10 (47.6) ^a	15 (24.6) ^c	.011
Aspartate aminotransferase, U/L	≤40	26.0 (18.0-38.3)	24.0 (17.3-36.0)	33.0 (29.0-47.0) ^a	25.0 (18.5-40.0) ^c	.031
Increased, n (%)		39 (23.5)	16 (19.0)	8 (38.1)	15 (24.6)	.178
Liver dysfunction (ALT or AST increased), n (%)		55 (33.1)	22 (26.2)	10 (47.6)	23 (37.7)	.111
Serum creatinine, μmol/L	45-84	72.5 (58.0-90.3)	69.0 (56.3-86.0)	71.0 (57.0-82.5)	75.0 (63.5-98.0) ^a	.002
Increased, n (%)		19 (11.4)	7 (8.3)	2 (9.5)	10 (16.4)	.308
Estimated glomerular filtration rate, ml/min/1.73m ²	>90	79.3 ± 24.5	83.5 ± 25.3	82.9 ± 21.1	72.1 ± 23.2 ^a	.016
>90, n (%)		68 (41.0)	40 (47.6)	10 (47.6)	18 (29.5)	.432
60-90, n (%)		59 (35.5)	29 (34.5)	8 (38.1)	22 (36.1)	.949
30-60, n (%)		33 (19.9)	12 (14.3)	2 (9.5)	19 (31.1) ^a	.019
<30, n (%)		6 (3.6)	3 (3.6)	1 (4.8)	2 (3.3)	1.000
Albumin, g/L	35-52	35.2 ± 5.6	36.3 ± 5.9	34.1 ± 5.4	34.1 ± 4.9 ^a	.034
Decreased, n (%)		89 (53.6)	34 (40.5)	15 (71.4) ^a	40 (65.6) ^a	.002
Lactate dehydrogenase, U/L	135-214	284.0 (227.0-382.3)	272.5 (210.8-328.8)	367.0 (276.0-521.5) ^a	273.0 (234.0-433.0) ^a	.002
Increased, n (%)		126 (75.9)	56 (66.7)	20 (95.2) ^a	50 (82.0) ^a	.009
Ferritin, ug/L ^d	30-400	636.6 (365.2-1306.7)	509.8 (263.2-1019.9)	1010.5 (558.6-1763.0) ^a	739.6 (411.6-1542.9) ^a	.002

(Continues)

TABLE 2 (Continued)

	Normal ranges	All patients (n = 166)	Group 1 (n = 84)	Group 2 (n = 21)	Group 3 (n = 61)	P value
Increased, n (%)		108 (65.1)	45 (53.6)	19 (90.5) ^a	44 (72.1) ^a	.004
D-dimer, µg/ml	<0.5	1.2 (0.5-2.4)	0.8 (0.5-1.9)	2.0 (0.5-14.4) ^a	1.8 (0.6-3.3) ^a	.005
Increased, n (%)		125 (75.3)	58 (69.0)	16 (76.2)	51 (83.6)	.133
Fibrinogen, g/L	2.00-4.00	5.0 ± 1.7	4.9 ± 1.5	4.6 ± 2.1	5.3 ± 1.8	.162
Increased, n (%)		81 (48.8)	37 (44.0)	8 (38.1)	36 (59.0)	.118
Fibrinogen degradation products, µg/ml ^d	<5.0	4.0 (4.0-7.8)	4.0 (4.0-5.6)	5.3 (4.0-150) ^a	5.4 (4.0-11.0) ^a	.007
Increased, n (%)		67 (40.4)	25 (29.8)	10 (47.6)	32 (52.5) ^a	.009
Creatine kinase, U/L ^d	≤170	74.0 (49.0-127.8)	73.0 (47.0-128.0)	69.0 (49.0-122.0)	77.0 (50.0-144.0)	.834
Increased, n (%)		31 (18.7)	14 (16.7)	4 (19.0)	13 (21.3)	.865
Cardiac troponin I, pg/ml ^d	≤15.6	5.0 (2.2-10.7)	4.0 (1.9-7.7)	4.1 (2.9-17.6)	7.2 (2.4-14.0)	.073
Increased		17 (10.2)	4 (4.8)	3 (14.3)	10 (16.4)	.057
Myoglobin, ng/ml ^d	≤106	54.8 (33.8-127.2)	44.7 (29.8-85.8)	80.8 (53.7-131.4) ^a	66.9 (32.5-148.5)	.025
Increased, n (%)		28 (16.9)	11 (13.1)	3 (14.3)	14 (23.0)	.287
Creatinine kinase MB, ng/ml ^d	≤3.4	0.8 (0.4-1.7)	0.7 (0.4-1.3)	1.3 (0.6-2.1)	1.0 (0.5-2.0)	.091
Increased, n (%)		6 (3.6)	2 (2.4)	1 (4.8)	3 (4.9)	.591
N-terminal pro-brain natriuretic peptide, pg/ml	<247	179.0 (67.0-457.0)	117.0 (42.5-290.8)	237.5 (95.5-704.5) ^a	251.0 (97.5-887.5) ^a	.001
Increased, n (%)		65 (39.2)	23 (27.4)	10 (47.6)	32 (52.5) ^a	.008
Erythrocyte sedimentation rate, mm/h ^d	0-15	33.0 (16.0-55.8)	25.0 (16.0-52.0)	33.0 (13.0-40.0)	40.0 (21.5-72.0) ^{a,c}	.017
Increased, n (%)		115 (69.3)	57 (67.9)	12 (57.1)	46 (75.4)	.123
Hypersensitive C-reactive protein, mg/L	>10, n (%)	26.2 (4.4-68.3)	13.9 (2.2-48.5)	43.3 (24.2-115.0) ^a	36.1 (8.2-112.5) ^a	.003
		103 (62.0)	45 (53.6)	17 (81.0) ^a	41 (67.2)	.040
Procalcitonin, ng/ml ^d	0.02-0.05	0.06 (0.03-0.14)	0.05 (0.03-0.10)	0.11 (0.03-0.29)	0.07 (0.03-0.34)	.097
<0.05, n (%)		81 (48.8)	46 (54.8)	7 (33.3)	28 (45.9)	.311
0.05-0.5, n (%)		69 (41.6)	33 (39.3)	10 (47.6)	26 (42.6)	.557
0.5-2.0, n (%)		13 (7.8)	5 (6.0)	2 (9.5)	6 (9.8)	.642
Interleukin-1β, pg/ml	<5.0	5.0 (5.0-5.0)	5.0 (5.0-5.0)	5.0 (5.0-5.0)	5.0 (5.0-5.0)	.435
Increased, n (%)		21 (12.7)	9 (10.7)	2 (9.5)	10 (16.4)	.525
Interleukin-2 receptor, U/ml	223-710	655.0 (426.5-1019.5)	656.5 (425.0-915.0)	909.0 (313.5-1388.0)	629.5 (492.8-1178.5)	.575
Increased, n (%)		73 (44.0)	34 (40.5)	12 (57.1)	27 (44.3)	.384
Interleukin-6, pg/ml	<7.0	14.1 (3.3-42.9)	12.9 (3.1-40.3)	15.8 (2.2-53.0)	15.9 (4.1-49.9)	.330
Increased, n (%)		106 (63.9)	49 (58.3)	14 (66.7)	43 (70.5)	.250
Interleukin-8, pg/ml	<62	11.0 (5.6-24.2)	10.0 (5.5-22.3)	10.8 (8.5-54.7)	11.3 (5.8-26.1)	.520
Increased, n (%)		12 (7.2)	4 (4.8)	5 (23.8) ^a	3 (4.9) ^c	.020

TABLE 2 (Continued)

	Normal ranges	All patients (n = 166)	Group 1 (n = 84)	Group 2 (n = 21)	Group 3 (n = 61)	P value
Interleukin-10, pg/ml	<9.1	5.0 (5.0-7.0)	5.0 (5.0-6.4)	5.0 (5.0-10.5)	5.0 (5.0-8.0)	.367
Increased, n (%)		28 (16.9)	10 (11.9)	6 (28.6)	12 (19.7)	.149
Tumour necrosis factor- α , pg/ml	<8.1	8.6 (6.0-12.0)	8.3 (6.0-12.0)	7.6 (5.9-10.0)	9.2 (6.0-12.8)	.594
Increased, n (%)		90 (54.2)	43 (51.2)	9 (42.9)	38 (62.3)	.182
CT scan		149 (89.8)	75 (89.3)	18 (85.7)	56 (91.8)	.715
Bilateral, n (%)						

Abbreviations: ALT, glutamic-pyruvic transaminase; AST, aspartate aminotransferase; CT, computed tomography; MB, myocardial band.

Data are n (%), mean \pm SD and median (interquartile range). 'Increased' means over the upper limit of the normal range and 'decreased' means below the lower limit of the normal range. The continuous variables with normal or non-normal distributions were compared among the three groups using ANOVA, independent t tests, or Kruskal-Wallis and Mann-Whitney tests. The χ^2 or Fisher exact test was used to compare categorical variables among the three groups. Group 1: control group; group 2: secondary hyperglycaemia group; group 3: diabetes group. The P value indicates differences among groups 1, 2 and 3.

^aP < .05 relative to group 1.

^bHbA1c was available for 33, 13 and 53 patients in groups 1, 2 and 3, respectively.

^cP < .05 relative to group 2.

^dData were not available for all patients: 159 results for fibrinogen degradation products and 154 results for ferritin, 160 results for creatinine kinase, 152 results for erythrocyte sedimentation rate, 165 results for myocardial enzyme tests, cytokine and procalcitonin results.

The patients in group 2 had the highest levels of LDH, which was ~ 1.4-fold those of the other two groups ($P = .001$ and $P = .05$, respectively), and over 95% of them had elevated LDH. Ferritin levels in groups 2 and 3 were significantly higher than that in group 1 ($P = .003$ and $P = .008$). The coagulation indexes such as D-dimer (1.8 [0.6-3.3] vs. 0.8 [0.5-1.9] $\mu\text{g/ml}$, $P = .003$) and the fibrinogen degradation products (FDP) level (5.4 [4.0-11.0] vs. 4.0 [4.0-5.6], $P = .004$) were both significantly higher in group 3 than in group 1. In addition, D-dimer and FDP levels in group 2 were comparable with group 3, but significantly higher than those in group 1 ($P = .034$ and $P = .036$). The level of myoglobin in group 2 was ~ 1.8-fold that in group 1 ($P = .023$). No significant differences were found in other enzymes indicating myocardial injury among the three groups. The patients in groups 2 and 3 had higher NT-proBNP levels compared with group 1 ($P < .05$ for both).

Finally, we also assessed inflammatory biomarkers. We found that patients in groups 2 and 3 had significantly higher sCRP than patients in group 1 ($P = .003$ and $P = .012$, respectively), but no significant difference was found between groups 2 and 3. The ESR in group 3 was much higher than those in groups 1 and 2 ($P < .05$ for both). There was no significant difference in PCT levels among the three groups ($P = .097$). Among all cytokines, we found that the increase in the ratio of IL-8 in group 2 was significantly higher than in groups 1 and 3 ($P < .05$ for both). The levels of other cytokines were comparable among the three groups.

3.3 | Treatment of diabetes before and after admission

Thirty-five patients in group 3 had a self-reported diabetes history. The prevalence of self-reported diabetes in our study was 21.1% (35/166). Therapy information regarding diabetes was unavailable for five patients (details were not provided in the medical records for four patients and one patient could not provide details of therapy). Three patients were not given antidiabetic therapy before admission. Among the 27 patients, eight (29.6%) received insulin therapy and continued to apply during hospitalization. Nineteen patients used simple oral antidiabetic drugs (OADs) to control blood glucose before admission, and eight (42.1%) of them moved to insulin therapy during hospitalization. Metformin (40.7%), α -glucosidase inhibitors (29.6%) and sulfonylureas (22.2%) were the most commonly taken OAD types among patients who used a simple OAD or an OAD combined with insulin therapy, and there was only one case treated with a dipeptidyl peptidase-4 (DPP-4) inhibitor before admission, and no sodium-glucose co-transporter-2 inhibitors were used before admission.

After admission, 37.7% (23/61) of patients in group 3 were treated with insulin (meal and/or basal insulin). Fifteen of the 23 patients had just started insulin therapy (four of them were diagnosed with diabetes after admission and started using insulin), and only two cases were treated with glucocorticoids during hospitalization, which might indicate that the deterioration of blood glucose status was mainly caused by COVID-19.

3.4 | Main interventions and outcomes

The main interventions and outcomes are shown in Table 3. More than 75% of patients received antiviral treatment and 46.4% of patients received antibiotic treatment. The percentage of patients receiving antibiotics was slightly higher in groups 2 and 3 than in group 1 (61.9% and 50.8% vs. 39.3%, $P = .121$). A total of 22.9% of patients were treated with systemic glucocorticoids (methylprednisolone) intravenously during hospitalization. While most patients were dosed at 1–2 mg/kg/day for ~3–7 days, four critically ill patients received 240–500 mg in pulse once a day for 3 days. No significant difference in glucocorticoid treatment was found among the three groups. Insulin therapy was more common in groups 2 and 3 compared with group 1 (14.3% vs. 0%, $P = .007$, and 36.1% vs. 0%, $P < .001$, respectively). No patients in any of the three groups developed ketoacidosis during hospitalization.

The proportion of critical patients in groups 2 and 3 was significantly higher than that in group 1 (38.1%, 32.8% vs. 9.5%, $P < .05$ for both). As of 4 April 2020, 15 patients (9.0%) were still hospitalized, 127 (76.5%) had been discharged and 24 (14.5%) had died. Patients in group 3 had comparatively longer hospital stays compared with patients in group 1 (26.3 ± 11.7 vs. 20.5 ± 11.3 days, $P = .011$). The rate of discharge was significantly lower in group 3 than in group 1 (63.9% vs. 84.5%, $P = .004$). However, there were no significant differences in the length of hospital stay and discharge rate between groups 2 and 3. The mortality rate of patients in groups 2 and 3 was greater than that in group 1 (14.3%, 21.3% and 9.5%, $P = .137$). Respiratory support was provided to 33 patients, all of whom started with non-invasive ventilation (NIV), owing to the difficulty in correcting oxygenation. Eleven of these patients switched to invasive ventilation (IV) but eventually died. There were significantly more patients needing mechanical ventilation support (NIV and IV) in groups 2 and

TABLE 3 Treatments and outcomes of coronavirus disease 2019 patients

	All patients (n = 166)	Group 1 (n = 84)	Group 2 (n = 21)	Group 3 (n = 61)	P value
Classification, n (%)					
Moderate	30 (18.1)	19 (22.6)	2 (9.5)	9 (14.8)	.264
Severe	100 (60.2)	57 (67.9)	11 (52.4)	32 (52.5)	.128
Critical	36 (21.7)	8 (9.5)	8 (38.1) ^a	20 (32.8) ^a	.001
Treatment, n (%)					
Antiviral treatment	126 (75.9)	64 (76.2)	13 (61.9)	49 (80.3)	.234
Antibiotic treatment	77 (46.4)	33 (39.3)	13 (61.9)	31 (50.8)	.121
Glucocorticoids	38 (22.9)	15 (17.9)	6 (28.6)	17 (27.9)	.294
Intravenous immunoglobulin therapy	29 (17.5)	12 (14.3)	4 (19.0)	13 (21.3)	.535
Tocilizumab	5 (3.0)	1 (1.2)	1 (4.8)	3 (4.9)	.319
Insulin therapy (meal and/or basal insulin)	25 (15.1)	0	3 (14.3) ^a	22 (36.1) ^a	<.001
Continuous renal replacement therapy	2 (1.2)	0	0	2 (3.4)	.371
Mechanical ventilation	33 (19.9)	8 (9.5)	8 (38.1) ^a	17 (27.9) ^a	.002
Non-invasive (face mask), n (%)	22 (13.3)	7 (8.3)	7 (33.3) ^a	8 (13.1)	.010
Off ventilator	6 (27.3)	1 (14.3)	3 (42.9)	2 (25.0)	.119
Invasive, n (%)	11 (6.6)	1 (1.2)	1 (4.8)	9 (14.8) ^a	.004
Off ventilator	0	0	0	0	
Treated in ICU, n (%)	7 (4.2)	1 (1.2)	1 (4.8)	5 (8.2)	.121
Outcomes					
Discharge from hospital, n (%)	127 (76.5)	71 (84.5)	17 (81.0)	39 (63.9) ^a	.014
Hospital stay, days	23.0 ± 12.2	20.5 ± 11.3	26.2 ± 14.8	26.3 ± 11.7 ^a	.026
Hospitalization, n (%)	15 (9.0)	5 (6.0)	1 (4.8)	9 (14.8)	.145
Death, n (%)	24 (14.5)	8 (9.5)	3 (14.3)	13 (21.3)	.137
From admission to death, days	14.9 ± 7.0	12.4 ± 6.3	16.0 ± 13.1	16.2 ± 6.1	.488
Composite outcomes, n (%)	34 (20.5)	9 (10.7)	8 (38.1) ^a	17 (27.9) ^a	.004

Data are n (%), mean ± SD, and median (interquartile range). The continuous variables with normal or non-normal distributions were compared among the three groups using ANOVA, independent t tests, or Kruskal–Wallis and Mann–Whitney tests. The χ^2 or Fisher exact test was used to compare categorical variables among the three groups. Composite outcomes include mechanical ventilation, treated in intensive care unit (ICU) and death. Group 1: control group; group 2: secondary hyperglycaemia group; group 3: diabetes group. The P values indicate differences among groups 1, 2 and 3.

^a $P < .05$ relative to group 1.

3 compared with patients in group 1 (38.1% vs. 9.5%, $P = .003$ and 27.9% vs. 9.5%, $P = .004$). The utilization rate of NIV in group 2 was significantly higher than that in group 1 (33.3% vs. 8.3%, $P = .007$). Six patients (one in group 1 [14.3%], three in group 2 [42.9%] and two [25.0%] in group 3) were successfully weaned from NIV and switched to oxygen masks ($n = 4$) or nasal cannula ($n = 2$) after achieving improved oxygenation. By contrast, 13 patients (13/17, 76.5%) using NIV in group 3 died, including nine who were switched to IV.

Approximately 30% of patients in groups 2 and 3 had composite outcomes, which were both significantly higher than for patients in group 1 ($P < .05$ for both). In logistic regression analysis adjusted for confounders, group 2 had a higher odds ratio (OR) of composite outcomes than group 1 (OR 5.47; 95% confidence interval [CI], 1.51-19.82, $P = .010$). The composite outcomes risk (OR 2.61; 95% CI 0.86-7.88, $P = .090$) in group 3 compared with group 1 was close to a statistically significant difference, and there was no significant difference in composite outcomes risk in group 2 compared with group 3 (OR 2.10; 95% CI 0.65-6.83, $P = .217$).

4 | DISCUSSION

We found that COVID-19 patients with diabetes and secondary hyperglycaemia were classified as more critical and had a ~2-5-fold greater composite outcomes risk compared with controls. Importantly, there are differences in these distinct COVID-19 patient subsets that should be considered during treatment.

Whether patients with diabetes are more susceptible to COVID-19 than non-diabetic patients is unclear. The Chinese Center for Disease Control and Prevention recently published the largest case study of COVID-19 in China showing that the prevalence of diabetes among the 44 672 confirmed cases was 5.3%.¹⁶ A recent meta-analysis¹⁷ of co-morbidities suggested that diabetes is found in ~8% of COVID-19 patients. The prevalence of diabetes in patients with COVID-19 mentioned above depended on a self-reported medical history of diabetes that varied depending on the status (mild, severe or critical) of each individual patient. The estimated standardized prevalence rate of diagnosed and undiagnosed diabetes in Chinese adults is 10.9% (95% CI, 10.4%-11.5%), and 6.9% (95% CI, 3.6%-4.3%) of the population received a new diagnosis by glycaemic biomarkers.¹⁸ Based on a self-reported medical history to make a diagnosis of diabetes, it is estimated that up to 50% of cases are undiagnosed, which could lead to an underestimation of the prevalence of diabetes.¹⁹ The prevalence of diabetes in COVID-19 (5.3%) is similar to results for the general population in epidemiological surveys (4%), according to a self-reported diabetes history. We speculated that susceptibility to COVID-19 was similar in patients with and without diabetes. The patients enrolled in our retrospective study were mainly severe and critical COVID-19 patients. The prevalence of diabetes was 21.1% based on a self-reported history of diabetes, but this increased to 36.7% if the diagnosis was based upon the 2009 American Diabetes Association standard,¹⁵ which was higher than the prevalence reported in similar recent studies.

Several reports have indicated that diabetes patients with COVID-19 tend to experience severe disease and a higher mortality rate. Wang et al²⁰ found that patients in the pulse oximeter oxygen saturation (SpO_2) < 90% group were more probable to have diabetes than those in the $SpO_2 \geq 90\%$ group (43% vs. 2%, $P < .001$). Wang et al³ and Gao et al⁷ reported that there appeared to be more patients with diabetes in the ICU than in the general ward (22.2% vs. 5.9%, $P = .009$ and 40.0% vs. 3.5%, $P = .005$, respectively), but some research results were inconsistent.^{4,6,12} The warning parameters for severe or critical patients are high levels of leukocytes, neutrophils,^{3,4} serum creatine,³ D-dimer,^{3,4,7} LDH,^{4,20} ferritin,⁸ CRP, PCT,^{3,4} IL-6⁷ and IL-10,²⁰ lymphocytopenia² and thrombocytopenia.²¹ Our study indicated that diabetic COVID-19 patients (group 3) had higher levels of leukocytes, neutrophils, serum creatine and LDH, lower levels of lymphocytes and eosinophils, and higher levels of inflammatory markers such as sCRP, ferritin, D-dimer and FDP, than patients in the control group. Most of the aforementioned changes indicated that patients with diabetes experience more severe disease than those in the control group.

In addition, the proportion of patients with diabetes among non-surviving patients was ~2-fold greater than among surviving patients. Guan et al¹ investigated composite endpoints (admission to the ICU, use of mechanical ventilation, or death) of COVID-19 patients. Out of these patients, the subset with diabetes was more probable to experience these endpoints than the subset without diabetes (26.9% vs. 6.1%). In Yang et al's study, the prevalence of diabetes was 22% in non-surviving COVID-19 patients, while it was 10% in surviving patients.² We found that the mortality rate as a result of COVID-19 in patients with diabetes was 21.3%, which was higher than the 9.5% mortality rate in the control group. We found an association of diabetes with composite outcomes in COVID-19 patients, but the result was not statistically significant (OR 2.61; 95% CI, 0.86-7.88), which may have been a consequence of the limited sample size with regard to obtaining robust positive results. Thus, our study suggests that pre-existing diabetes might increase the risk of composite outcomes in patients with COVID-19. Therefore, attention should be paid to diabetic patients with COVID-19, including patients with undiagnosed diabetes.

There are multiple causes for the high rates of severe and critical cases and high mortality in COVID-19 patients with diabetes. Among the three groups in our study, diabetic COVID-19 patients had the highest proportions of co-morbidities, such as hypertension and cardiovascular disease, and the prevalence of cardiovascular disease was almost statistically significant, possibly because of the small sample size. In our study, the ratio of $eGFR < 60$ mL/min/1.73m², and the higher levels of serum creatine and NT-proBNP in group 3, all indicate poor basic kidney and heart function in patients with diabetes. This supports the notion that chronic co-morbidities in patients with COVID-19 are risk factors for severe cases compared with non-severe cases.¹⁷ In addition, as a type of subclinical chronic inflammation, diabetes shares some common characteristics with infectious diseases, such as pro-inflammatory status and attenuation of the innate immune response. Furthermore, the function of T cells, neutrophils,

macrophages and lymphocytes is reduced in patients with diabetes, resulting in damaged humoral immune systems and rendering these individuals more susceptible to a range of infectious diseases.²² In COVID-19, the virus activates immunocytes and induces the secretion of inflammatory cytokines and chemokines (i.e. the 'cytokine storm') into pulmonary vascular endothelial cells and other organs.^{4,23} In our study, the cytokine storm—a common reaction in COVID-19 patients—was not as evident in diabetic COVID-19 patients as in the control group. Moreover, in our study, more patients with diabetes had lymphocytopenia, leukocytosis, neutrophilia, elevated sCRP levels and a higher proportion of antibiotic therapy during hospitalization. We speculate that COVID-19 patients' conditions would worsen with concomitant bacterial infections. Therefore, we suggest that the severity of the disease and high risk of composite outcomes of COVID-19 patients with diabetes are associated with chronic co-morbidities, weak immune responses, and the potential for concurrent bacterial infection. Because the sample ($n = 27$) of antidiabetic treatment cases before admission was small in our study, and especially as DPP-4 inhibitors were rarely administered (i.e. only one case), the relationship between OADs and the susceptibility and severity of diabetic COVID-19 is currently uncertain.

Our study suggests that COVID-19 patients with secondary hyperglycaemia constitute another population with poor prognoses, which requires additional attention. Interestingly, there are both commonalities and differences between COVID-19 patients with secondary hyperglycaemia and those with diabetes. Most peculiarities of group 2 patients, such as higher levels of leukocytes, neutrophils, sCRP and NT-proBNP, lower levels of eosinophils and coagulopathy, and a higher proportion classified as critical, were different to those of group 1 patients, but were similar to those of patients with diabetes, indicating the severity and poor prognoses of the disease (longer hospital stays, a higher percentage of patients needing assisted ventilation, and more composite outcomes). Nevertheless, COVID-19 patients with secondary hyperglycaemia appear to experience more liver damage, higher levels of LDH, and an increased IL-8 ratio, than those patients with diabetes.

A significantly higher in-hospital mortality rate has been reported for patients with new hyperglycaemia (e.g. stress hyperglycaemia and undiagnosed diabetes), who also had poorer outcomes than patients with a previous history of diabetes and subjects with normoglycaemia.²⁴ Increased gluconeogenesis and decreased glycogenolysis because of increased secretion of counter-regulatory hormones are believed to be the potential mechanisms underlying stress hyperglycaemia. On the other hand, autopsies of COVID-19 patients revealed islet cell degeneration,²⁵ which might indicate that SARS-CoV-2 could cause islet cell damage or other possibilities.

The SARS-CoV-2 and SARS Coronaviruses (SARS-CoVs) genome-wide similarity is ~ 79%.²⁶ Both viruses can enter cells through angiotensin converting enzyme 2 (ACE2),²⁷ which has been found in a variety of human tissues, such as the lung and pancreas.²⁸ Acute damage to pancreatic beta cells because of SARS-CoV-2 followed by hyperglycaemia might occur in this systemic illness, similar to the process in patients with SARS.¹¹ In our study, the proportion of patients with

increased IL-8 was much higher in group 2 than in those patients with diabetes. Hyperglycaemia and high levels of cytokines both reflect the severity of viral infection and the involvement of multiple systems. Moreover, the severity of COVID-19 in patients with secondary hyperglycaemia, even given the highest proportion of NIV in that group, still had a high probability (close to 50%) of withdrawal compared with the control and diabetes groups, matching the characteristics of acute viral injury.

Because no specific antiviral drugs have been confirmed as effective, the clinical management of hospitalized patients with COVID-19 is focused on supportive treatment on the complications. To reduce inflammation-induced lung injury as a result of the abundance of cytokines in COVID-19 patients, glucocorticoids are frequently used to treat severe and critically ill patients. Glucocorticoid usage as part of COVID-19 treatment regimens fluctuates from 14.9% to 58%.^{1-5,20} However, the risk-benefit ratio for treatment with glucocorticoids is unclear, especially in patients with hyperglycaemia. A recent study reported by researchers in Wuhan showed that systemic corticosteroid therapy has not shown significant benefits.²⁹ We believe that corticosteroids should not be routinely recommended for COVID-19 patients with diabetes. These patients might not experience obvious cytokine storm, have weak immune responses, and are susceptible to secondary bacterial infections, especially considering the aggravating effects of glucocorticoids on hyperglycaemia; therefore, glucocorticoids should not be administered unless they are indicated for other reasons (e.g. refractory septic shock, rapid progression on imaging and overactivation of the human inflammatory response).¹⁴ Treatment for hyperglycaemia might be an important supportive treatment for these patients. However, given the similarities and differences between the clinical profiles of COVID-19 patients with secondary hyperglycaemia and those with diabetes, strategies for using glucocorticoids might differ and require extra caution.

The diagnosis of diabetes in our study was not limited to a self-reported history of diabetes, but also included the levels of FPG and/or HbA1c to minimize the possibility of underestimating the prevalence of diabetes in COVID-19 patients. It should be noted that compared with a high FPG level, an HbA1c cutoff of 6.5% identifies more patients with undiagnosed diabetes.³⁰ Patients with secondary hyperglycaemia were also included and analysed as a new group in this study. Taking into account the high prevalence of chronic co-morbidities, hypoxemia, the higher incidence of heart and kidney damage in patients with diabetes, and considering the greater risk of liver dysfunction in COVID-19 patients with secondary hyperglycaemia, it is recommended to use an insulin regimen in patients with poorly controlled hyperglycaemia.³¹

Our research has several limitations. First, only 166 patients were included (all of whom were inpatients) and therefore the study sample was not large. In addition, mild COVID-19 patients were not admitted to our centre, which could have led to a biased understanding of the disease. Third, as a retrospective study, the data in this study can only provide a preliminary assessment of the clinical profiles and prognosis of diabetes and secondary hyperglycaemia patients with COVID-19. Finally, because of the small number of patients with diabetes, the

relationship between some special antidiabetic drugs and severe and critical COVID-19 cases has not been observed. Larger studies will be needed to validate our findings.

In conclusion, the higher severity of disease and mortality rate in COVID-19 patients with diabetes may be a result of chronic co-morbidities, a weak immune response, and a higher risk of secondary bacterial infections, instead of the severe cytokine storm caused by COVID-19, which might indicate the need for different therapeutic strategies. However, there are differences between secondary hyperglycaemia and diabetes; secondary hyperglycaemia appears to be the cause of a more severe inflammation reaction and multiple organ damage induced by the virus, and patients may require additional attention and different treatments. Clinicians should pay more attention to the blood glucose status of patients (even patients without a history of diabetes) with COVID-19, as it may be indicative of a poor prognosis. We believe that our study provides evidence that blood glucose status should be viewed as a key metric in the development of an effective public health strategy to mitigate COVID-19-associated poor prognoses.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Y.G., Y.Z., J.Z., J.M. and H.Z. designed the study. Y.Z. and N.Y. performed the literature review. Y.Z. collected, interpreted and analysed the clinical data. Y.C. and X.Z. organized the clinical data and Y.Z. and Y.G. summarized all the data. Y.Z. and Y.G. drafted the manuscript. Y.G., H.L., J.Z., X.G. and X.L. revised the final manuscript. Y.G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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