

Clinical Characteristics and Glucocorticoids Efficacy in COVID-19 Patients with Type 2 Diabetes: A Multicenter Retrospective Study

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Background: Type 2 diabetes mellitus (T2DM) patients infected with coronavirus disease 2019 (COVID-19) are at a higher risk of experiencing poorer prognoses and increased mortality. Glucocorticoids are recommended for the treatment of COVID-19, especially in patients with severe disease. However, the efficacy and safety of glucocorticoids in COVID-19 patients with T2DM remain a subject of debate.

Methods: We conducted a multicenter, retrospective cohort study of hospitalized patients with T2DM and confirmed COVID-19 admitted between November 1, 2022 and January 31, 2023. Data on clinical manifestations, treatment strategies, and clinical outcomes were systematically collected and rigorously evaluated.

Results: A total of 624 COVID-19 patients with T2DM were enrolled, comprising 259 patients with severe disease and 365 with non-severe disease. Compared with the non-severe group, the severe group demonstrated significantly elevated levels of inflammatory markers and more extensive multi-organ dysfunction. Multivariate logistic regression identified advanced age, male sex, cerebrovascular disease history, and poor fasting glucose control as independent predictors of progression to severe illness. Among patients with severe disease, glucocorticoid therapy was significantly associated with reduced in-hospital mortality and a shorter median length of stay; this association remained robust after adjustment for baseline glycemic status. Six-month post-discharge follow-up revealed no significant between-group differences in the incidence of long COVID-19 or interstitial pneumonia; however, among patients in non-severe group, those who received glucocorticoids exhibited a higher incidence of long COVID-19.

Conclusion: Glucose control is of particular importance for COVID-19 patients with T2DM. In mild or moderate cases, systemic use of glucocorticoid therapy should be strictly evaluated. In severe or critical cases, cautious, appropriate use of glucocorticoids may be associated with improved short-term prognosis and reduced mortality.

Keywords: COVID-19, type 2 diabetes, glucocorticoids, multicenter retrospective study

Introduction

SARS-CoV-2, a coronavirus of the β genus, is primarily transmitted through respiratory droplets and close contact, leading to the global pandemic in 2020. Diabetes mellitus, a prevalent and chronic condition, represents one of the major public health challenges. Researches have demonstrated that diabetic patients exhibit impaired immune responses, rendering them more susceptible to severe infections and resulting in poorer prognoses compared to non-diabetic individuals.^{1,2} Li et al reported that 21.4% of hospitalized patients with COVID-19 had preexisting diabetes mellitus; this prevalence was significantly elevated in severe and critical cases, reaching 28.9% and 34.6%, respectively.³ Among these patients, suboptimal glucose control is associated with an increased likelihood of ICU admission and adverse

clinical outcomes.⁴ Mechanistically, persistent hyperglycemia may exacerbate systemic inflammation and impair antiviral immune responses, thereby contributing to progression to severe or critical illness.^{5,6} This indicates that diabetes is a significant risk factor for severe COVID-19. Moreover, studies have shown that the excessive inflammatory response induced by SARS-CoV-2 and the decreased viral clearance ability in the early stage of infection are associated with disease progression and rapid mortality.⁷ Therefore, in addition to early antiviral treatment, glucocorticoids are recommended for treating COVID-19 patients, particularly those with severe disease. The RECOVERY trial demonstrated that dexamethasone can reduce mortality among COVID-19 patients requiring respiratory support due to respiratory failure.⁸ However, the RECOVERY trial lacked stratified analysis for specific risk factors, and patients with diabetes constituted only a small portion of the study population. Additionally, glucocorticoid use may exacerbate stress-induced hyperglycemia in patients with type 2 diabetes mellitus (T2DM) infected with SARS-CoV-2, further compromising their immune function. This increases the risk of uncontrolled infection and disease aggravation. Nevertheless, current international clinical guidelines do not provide specific, tailored recommendations on the safe and appropriate use of glucocorticoids in COVID-19 patients with T2DM, especially regarding patient selection, dosing, and concomitant glycemic management. Consequently, there is an urgent need to investigate the benefits of glucocorticoids in reducing inflammatory reactions in COVID-19 patients with T2DM. This study systematically characterizes the clinical features of patients with COVID-19 and T2DM, evaluates the efficacy of glucocorticoid therapy in this population, and assesses long-term outcomes including interstitial pneumonia during the 6-month post-discharge follow-up. Our aim is to support the early identification of high-risk cases and inform the development of personalized treatment strategies.

Methods

Study Design and Inclusion Criteria

A multicenter retrospective study was conducted to analyze the clinical characteristics of adult patients (≥ 18 years old) with T2DM who were hospitalized due to COVID-19 between November 1, 2022 and January 31, 2023. Data were collected from the First Affiliated Hospital of Guangxi Medical University and the Guangxi Zhuang Autonomous Region People's Hospital. This research was conducted with approval from the Research Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2024-E282-01) and the Peoples Hospital of Guangxi Zhuang Autonomous Region (KY-IIT-2023-107). All research procedures adhered strictly to the principles outlined in the Declaration of Helsinki.

Oral glucose tolerance test failed to differentiate between hyperglycemia caused by T2DM and that resulting from the infection, as infections can elevate blood glucose levels. Therefore, we included patients with known T2DM history.

Data Collection

These data, encompassing demographic data, medical history of chronic disease, clinical characteristics, laboratory findings, imaging manifestations, treatment modalities and clinical outcomes, were systematically collected and analyzed from the hospital's electronic medical record system. Additionally, 6-month post-discharge follow-up data were collected to evaluate long-term outcomes, including the incidence of long COVID-19 syndrome and radiological findings of interstitial pneumonia—specifically, both newly developed interstitial pneumonia and exacerbation of pre-existing interstitial pneumonia were included in our statistical analysis. Follow-up information was obtained through patients' outpatient records or telephone interviews, and any occurrence of the aforementioned symptoms or imaging changes at any time within 6 months after discharge was recorded.

Grouping and Endpoints

The diagnosis and clinical classification of COVID-19 patients were conducted in accordance with “Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia Version 9 (Trial)” established by the Chinese National Health Commission, categorizing patients into mild, moderate, severe, and critical conditions ([Supplement Table 1](#)).⁹ Non-severe group included those with mild or moderate conditions, while severe group encompassed

individuals with severe or critical conditions. Additionally, glucocorticoid therapy was identified as the primary exposure factor leading to patient stratification into two cohorts: glucocorticoid cohort and no glucocorticoid cohort.

The primary outcomes included mortality, length of hospital stay, and rate of intensive care unit (ICU) monitoring. Secondary outcomes comprised the incidence of long COVID-19 syndrome, defined as the presence of any persisting symptoms at 6-month follow-up, and the occurrence of interstitial pneumonia identified through CT scans or radiography.

Statistical Analysis

Continuous variables were expressed as median and interquartile ranges (IQRs) due to their non-normal distribution, while categorical variables were presented as percentage (%). All included variables had a missing data rate of <10%, and missing data were handled using listwise deletion (the default method in SPSS), with only patients with complete data for all analyzed variables retained for statistical analysis. For the same reason, the *t*-test or nonparametric Wilcoxon test for independent samples was employed to assess the difference in continuous variables between groups. The chi-squared test was utilized to examine associations between qualitative or dichotomized variables. In cases where expected cell counts were five or less, the Fisher exact test was substituted for the chi-squared test. Univariable logistic analysis was performed on all baseline variables, and those with a significance level of $P < 0.05$ were included in the multivariable logistic analysis to identify risk factors associated with the severity of COVID-19 patients with T2DM. The statistical analyses were performed using SPSS (Version 26.0), and the figures were plotted using software package R (version 4.2.3). A significance level of $p < 0.05$ was considered statistically significant.

Result

Demographic and Clinical Features of COVID-19 Patients with T2DM

Among the 643 patients diagnosed with COVID-19 and diabetes, a total of 624 individuals with a documented history of T2DM were included in this multicenter retrospective study (Figure 1). The patients' ages ranged from 31 to 102 years, with a median age of 73 (65, 82), and the male patients accounted for a higher proportion (429/624, 74.9%). The median body mass index (BMI) was 24.1 kg/m² (22.1, 26.5), with 222 patients (35.6%) classified as overweight or obese (BMI ≥ 24 kg/m²). Moreover, the most common comorbidity was hypertension (426/624, 68.3%), followed by cerebrovascular diseases (217/624, 34.8%).

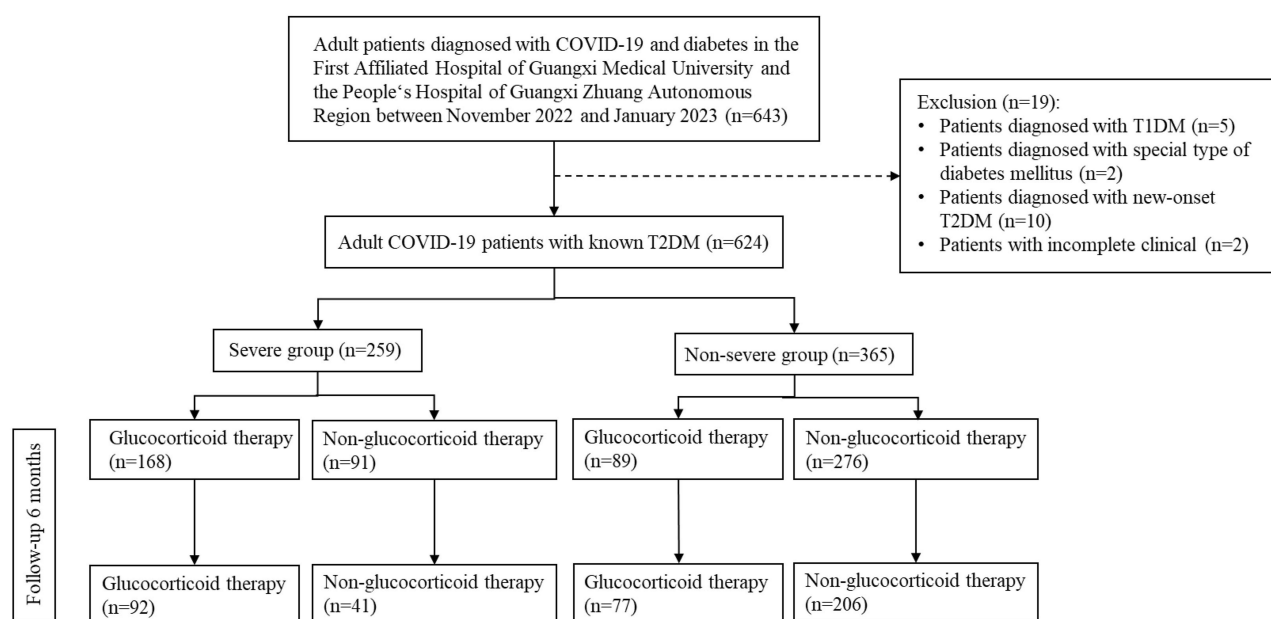


Figure 1 Flow diagram showing the enrolment of COVID-19 inpatients with T2DM.

According to the “Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia Version 9 (Trial)”, out of 624 cases, 89 (14.3%) were classified as mild, 277 (44.4%) as moderate, 140 (22.4%) as severe, and 118 (18.9%) as critical. The most common symptoms observed were cough (527/624, 84.5%) and anorexia (398/624, 63.8%), followed by dyspnea (351/624, 56.3%), fever (350/624, 56.1%), fatigue (265/624, 42.5%), nausea and vomiting (88/624, 14.1%), sore throat (64/624, 10.3%), and muscle soreness (51/624, 8.2%). Among the patients, 150 (24.0%) individuals developed respiratory failure, while altered consciousness was observed in 64 (10.3%) patients and shock was reported in 58 (9.3%) patients.

Clinical Characteristics in the Severe and Non-Severe Groups

Demographic and Clinical Features of the Severe and Non-Severe Groups

The demographic and clinical features of the patients are shown in Table 1. There were 259 cases (41.5%) in the severe group and 365 cases (58.5%) in the non-severe group. The proportion of male patients in the severe group (74.9%) was significantly higher than that in the non-severe group (64.4%) ($p < 0.01$). The median age of patients in the severe group and the non-severe group was 75 (67, 84) years and 72 (63, 80) years, suggesting that the median

Table 1 Demographic and Clinical Characteristics of Patients

Characteristics	Severe N=259	Non-Severe N=365	P-value
Age (years)	75 (67, 84)	72 (63, 80)	<0.001
Gender, male, n (%)	194 (74.9)	235 (64.4)	0.005
Non-smoker, n (%)	199 (76.8)	292 (80.0)	0.341
BMI (kg/m ²)	23.9 (21.4, 26.0)	24.3 (22.4, 26.6)	0.115
Comorbidity, n (%)			
Hypertension	182 (70.3)	244 (66.8)	0.366
Cardiovascular disease	77 (29.7)	110 (30.1)	0.913
Cerebrovascular diseases	113 (43.6)	104 (28.5)	<0.001
Pulmonary disease	27 (10.4)	28 (7.7)	0.232
Chronic kidney disease	43 (16.6)	64 (17.5)	0.761
Liver disease	4 (1.5)	15 (4.1)	0.065
Rheumatoid disease	14 (5.4)	14 (3.8)	0.351
Malignancy	36 (13.9)	39 (10.7)	0.224
Symptoms, n (%)			
Cough	230 (88.8)	297 (81.4)	0.012
Dyspnea	202 (78.0)	149 (40.8)	<0.001
Sore throat	24 (9.3)	40 (11.0)	0.492
Nausea and vomiting	32 (12.4)	56 (15.3)	0.291
Anorexia	184 (71.0)	214 (58.6)	0.001
Fever	174 (67.2)	176 (48.2)	<0.001
Fatigue	111 (42.9)	154 (42.2)	0.868

(Continued)

Table 1 (Continued).

Characteristics	Severe N=259	Non-Severe N=365	P-value
Muscle soreness	19 (7.3)	32 (8.8)	0.520
Laboratory Finding			
White blood cell ($\times 10^9/L$)	10.28 (7.0, 14.1)	6.9 (5.3, 8.8)	<0.001
Neutrophil ($\times 10^9/L$)	8.5 (5.4, 12.9)	4.8 (3.4, 6.6)	<0.001
Lymphocyte ($\times 10^9/L$)	0.7 (0.5, 1.0)	1.2 (0.9, 1.6)	<0.001
Platelet ($\times 10^9/L$)	210.0 (141.0, 274.0)	241.5 (176.8, 313.8)	<0.001
Hemoglobin (g/L)	113.7 (93.0, 132.0)	120.0 (103.2, 135.0)	0.002
C-reactive protein (mg/L)	106.2 (52.7, 175.6)	25.2 (6.2, 63.3)	<0.001
Interleukin-6 (pg/mL)	68.5 (16.7, 244.7)	11.6 (3.6, 30.0)	<0.001
Serum ferritin (ng/mL)	870.2 (548.0, 1500.0)	456.5 (288.5, 905.9)	<0.001
ESR (mm/h)	63.0 (40.5, 85.5)	51.0 (25.5, 79.0)	0.019*
Fasting blood glucose (mmol/L)	8.2 (6.2, 13.2)	7.3 (5.7, 10.0)	0.003
Glycosylated hemoglobin (%)	7.6 (6.8, 9.4)	7.6 (6.7, 9.3)	0.813
Albumin (g/L)	30.1 (26.8, 33.7)	35.4 (31.9, 38.7)	<0.001
AST (U/L)	32.0 (21.0, 54.0)	23.0 (17.0, 32.0)	<0.001
ALT (U/L)	24.0 (15.0, 47.0)	20.0 (13.0, 29.8)	<0.001
Cr (mL/min)	107.0 (72.0, 204.0)	84.0 (64.8, 121.7)	<0.001
CK-MB (U/L)	17.0 (13.0, 25.0)	14.0 (11.0, 17.0)	<0.001
PT (S)	14.0 (12.7, 15.2)	13.1 (11.9, 13.8)	<0.001
APTT (S)	36.2 (32.3, 41.9)	34.0 (30.3, 37.8)	<0.001
D-dimer (ng/mL)	1552.5 (684.0, 4645.5)	632.0 (279.0, 1179.0)	<0.001
CD3+ lymphocyte count (/ μ L)	344.0 (200.0, 579.0)	708.0 (411.0, 1090.0)	<0.001
CD4+ lymphocyte count (/ μ L)	177.0 (109.0, 369.0)	418.0 (259.0, 659.0)	<0.001
CD8+ lymphocyte count (/ μ L)	119.0 (71.0, 194.0)	262.0 (131.0, 424.0)	<0.001
Oxygenation index (mmHg)	200.5 (124.3, 253.3)	388.0 (338.0, 452.0)	<0.001

Note: Data were as median (IQR) or number (proportion).

Abbreviations: BMI, body mass index; ESR, Erythrocyte sedimentation rate; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK-MB, creatine kinase isoenzyme MB; PT, plasma prothrombin; APTT, activated partial thromboplastin time.

age of patients in the severe group was higher ($p < 0.001$). The median BMI was 23.9 kg/m^2 (21.4, 26.0) in the severe group and 24.3 kg/m^2 (22.4, 26.6) in the non-severe group. In comparison with the non-severe group, the severe group had a higher proportion of patients with previous cerebrovascular disease (28.5% vs. 43.6%, $p < 0.001$), while there was no significant difference between the two groups regarding the presence of hypertension, cardiovascular disease, pulmonary disease, chronic kidney disease, liver disease, rheumatoid disease and malignancy ($p > 0.05$).

The patient's condition was assessed through a series of laboratory tests, encompassing the detection of inflammatory markers, kidney function indicators, liver function biomarkers, coagulation profile markers, and other hematological parameters in response to COVID-19 development. The severe group exhibited a significant increase in white blood cell count (WBC) and neutrophil (Neu) count, while lymphocyte (Lym) count showed a significant decrease. In contrast, the non-severe group demonstrated median values within the normal range for WBC count, Neu count, and Lym count. Regarding inflammatory markers, C-reactive protein, procalcitonin, interleukin-6 (IL-6), serum ferritin, and erythrocyte sedimentation rate were significantly elevated in both severe and non-severe patients; however, the increase was more pronounced in severe patients with statistical significance observed ($p < 0.05$). The blood glucose parameters, including fasting blood glucose (FBG) and glycosylated hemoglobin, exceeded the normal range upon admission in both groups. Moreover, the severe group exhibited a significantly higher median FBG level compared to the non-severe group ($p < 0.05$). The serum albumin levels in the severe group and non-severe group exhibited varying degrees of decrease, with a more significant reduction observed in the severe group. Additionally, hemoglobin levels were found to be lower than normal. In comparison to patients in the non-severe group, the severe group showed increased levels of Serum creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase isoenzyme MB (CK-MB), plasma prothrombin time (PT), activated partial thromboplastin time (APTT) and D-dimer. Platelet count, oxygenation index, CD3⁺ lymphocyte count, CD4⁺ lymphocyte count, and CD8⁺ lymphocyte count were significantly lower in the severe group compared to the non-severe group.

Regarding imaging assessment, a total of 624 patients were included in the analysis; among them, chest CT or radiography was not performed in 10 patients (4 in the severe group and 6 in the non-severe group) due to clinical constraints. Among the 614 patients with available imaging data, 557 (91.5%) exhibited abnormal chest CT findings. In the severe group, bilateral lung involvement was observed in 98.0% of patients who underwent imaging, unilateral lung involvement in 1.6%, no pulmonary involvement in 0.4%, and bilateral pleural effusions in 40.0%. In the non-severe group, bilateral lung involvement was present in 78.3% of imaged patients, unilateral lung involvement in 6.1%, no pulmonary involvement in 15.6%, and bilateral pleural effusions in 15.0%. In COVID-19 patients with T2DM, pulmonary imaging revealed that bilateral lung infection was predominantly observed along with occasional presence of bilateral pleural effusions, particularly among those classified as severe cases; this difference was statistically significant ($p < 0.001$).

Risk Factors for Identifying the Severity of COVID-19 Patients with T2DM

As shown in [Supplementary Table 2](#), we conducted a univariable logistic analysis on sixteen potential factors. The result determined five critical illness-related variables, including age, sex, history of cerebrovascular disease, FBG, and diastolic blood pressure. The statistically significant indicators from the univariate logistic analysis were included in the multivariate regression analysis. The results demonstrated that age (OR=1.03, 95% CI 1.01–1.04, $p < 0.01$), sex (OR=1.67, 95% CI 1.06–2.67, $p < 0.05$), cerebrovascular disease history (OR=1.56, 95% CI 1.00–2.42, $p < 0.05$), and FBG (OR=1.08, 95% CI 1.03–1.13, $p < 0.01$) were independent predictors for identifying the severity of COVID-19 patients with T2DM ([Figure 2](#)).

Treatments and Outcomes

Among the patients in the severe group, 99.6% required respiratory support, with 31.0% needing invasive mechanical ventilation and 69.0% requiring non-invasive mechanical ventilation. In comparison, 70.4% of the patients in the non-severe group required non-invasive mechanical ventilation, while none required invasive mechanical ventilation. There were significant differences between the two groups in the use of antiviral, antibacterial, anticoagulant, and glucocorticoid therapies, with higher usage rates in the severe group (all $p < 0.01$). Of the total patients, 361 (57.9%) received antiviral drugs, with a significantly higher proportion in the severe group (74.9%, $n=194$) compared to the non-severe group (45.8%, $n=167$). Given that viral infections often predispose patients to secondary bacterial infections, 82.1% ($n=512$) of patients received antibacterial therapy, including 97.3% ($n=252$) of severe patients versus 71.2% ($n=260$) of non-severe patients. Furthermore, systemic glucocorticoid therapy was administered to 168 patients in the severe group and 89 in the non-severe group, while anticoagulant therapy was provided to 165 patients in the severe group and 97 in

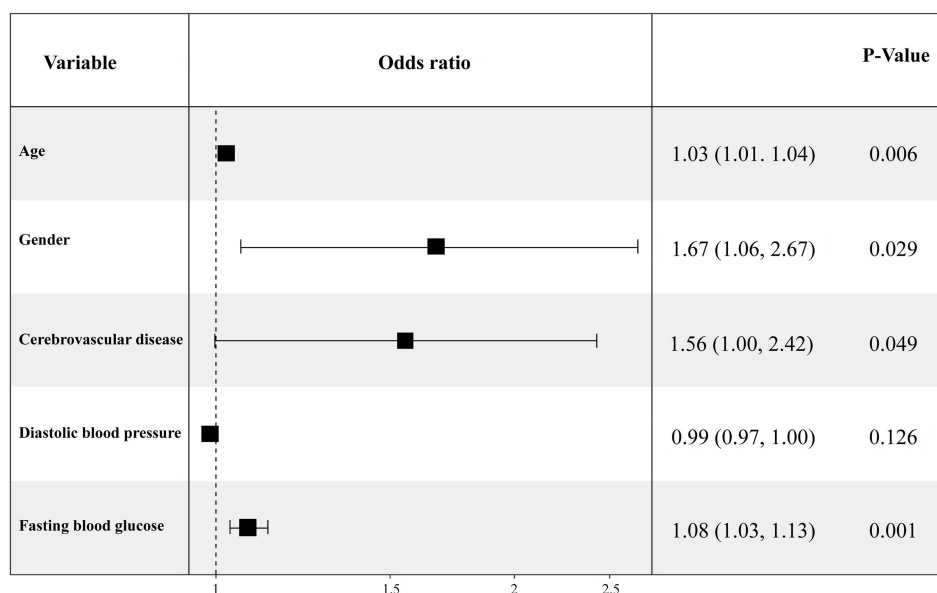


Figure 2 Independent risk factors in COVID-19 patients with T2DM.

the non-severe group. Regarding blood glucose control, approximately 90% of patients in both groups required medication for glycemic management.

The median length of hospital stay was 10 days (7, 15) in the non-severe group and 16 days (10, 23) in the severe group, indicating a significantly longer duration for the severe group ($p < 0.001$). Statistical analysis revealed that patients in the severe group were at a higher risk of clinical deterioration ($p < 0.001$) and had poorer prognoses. Specifically, 94 patients in the severe group required ICU admission due to disease progression, with over half ($n = 65$, 69.1%) subsequently succumbing to their illness. In contrast, there were no deaths in the non-severe group, while 91 patients (35.1%) in the severe group died. The results were shown in Table 2. Notably, among the 91 deceased patients, 90 experienced severe pneumonia and respiratory failure, 57 suffered from circulatory failure, and 71 exhibited multiple organ dysfunction.

Table 2 Treatment and Clinical Outcomes

	Severe N=259	Non-Severe N=365	P-value
Treatment			
Respiratory supportive treatment	259 (99.6)	257 (70.4)	<0.001
Invasive mechanical ventilation, n (%)	80 (31.0)	0 (0)	<0.001
Non-invasive mechanical ventilation, n (%)	178 (69.0)	257 (70.4)	0.652
Antiviral, n (%)	194 (74.9)	167 (45.8)	<0.001
Antibacterial, n (%)	252 (97.3)	260 (71.2)	<0.001
Anticoagulant, n (%)	165 (63.7)	97 (26.6)	<0.001
Glucocorticoid, n (%)	168 (64.9)	89 (24.4)	<0.001
Hypoglycemic, n (%)	235 (90.7)	328 (89.9)	0.781

(Continued)

Table 2 (Continued).

	Severe N=259	Non-Severe N=365	P-value
Outcomes			
Death, n (%)	91 (35.1)	0 (0)	<0.001
Require ICU stay	94 (36.3)	0 (0)	<0.001
Length of hospital stay (day)	16 (10, 23)	10 (7, 15)	<0.001

Abbreviation: ICU, intensive care unit.

Efficacy of Glucocorticoids in COVID-19 Patients with T2DM

In the non-severe group, patients treated with systemic glucocorticoids had a median hospital stay of 11 days (8, 17 days), compared to 9 days (7, 14 days) for those not receiving systemic glucocorticoids ($p<0.05$). Among these patients requiring respiratory support, the median length of hospital stay was 11 days (9, 17 days) for those treated with glucocorticoids versus 10 days (8, 15 days) for those who did not receive glucocorticoids ($p=0.069$). In the severe group, the mortality rate for patients treated with systemic glucocorticoids was significantly lower at 29.2% compared to 46.2% for those not treated with glucocorticoids ($p<0.01$) (Table 3). Specifically, among the 228 patients in severe group who had complete FBG data, 175 exhibited poor blood glucose control (glycosylated hemoglobin $> 7\%$ or FBG ≥ 7 mmol/L upon admission), while 53 had adequate blood glucose control. Notably, within the subgroup of patients with poor blood glucose control, those receiving systemic glucocorticoids demonstrated a significantly lower mortality rate of 25.8% compared to 49.1% for those who did not receive glucocorticoid treatment ($p<0.01$).

Six-Month Follow-Up Outcomes for Long COVID-19 Syndrome and Interstitial Pneumonia

A total of 416 patients (66.7%) were followed up for 6 months post-discharge, comprising 133 patients in the severe group and 283 patients in the non-severe group (Figure 1). A total of 208 patients (33.3%) were lost to follow-up, defined as failure to complete scheduled assessments either by telephone interview or during a scheduled outpatient visit. There was no statistically significant difference in the incidence of long COVID-19 symptoms or interstitial pneumonia, as suggested on chest CT, between the two groups. In the severe group, a total of 92 patients received glucocorticoid treatment. Among these patients, 6.5% developed long COVID-19 syndrome, and 5.4% exhibited interstitial pneumonia on CT scans. In contrast, among the 41 patients who did not receive glucocorticoids, 4.9% developed long COVID-19 syndrome, and none showed signs of interstitial pneumonia on chest CT. The differences between these two groups were not statistically significant. Furthermore, in the non-severe group, the incidence of long COVID-19 syndrome was higher among patients who received glucocorticoids compared to those who did not (10.4% vs. 3.4%, $p<0.05$). However, there

Table 3 Clinical Outcomes of Patients Treated with or without Systemic Glucocorticoids

Outcomes	Severe N=259			Non-Severe N=365		
	with Glucocorticoids N=168	without Glucocorticoids N=91	P-value	with Glucocorticoids N=89	without Glucocorticoids N=276	P-value
Length of hospital stay (day)	16 (10, 23)	14 (8, 22)	0.094	11 (8, 17)	9 (7, 14)	0.014
Death, n (%)	49 (29.2)	42 (46.2)	0.006	0	0	

was no statistically significant difference in the prevalence of interstitial pneumonia between the two groups ([Supplementary Table 3](#)).

Discussion

T2DM is the second most prevalent comorbidity following hypertension among hospitalized COVID-19 patients.¹⁰ Research has demonstrated that T2DM is a significant risk factor associated with the severity of COVID-19, and severe cases can rapidly deteriorate into acute respiratory distress syndrome (ARDS), multiple organ failure, and even death.¹¹ Therefore, this study aims to summarize the clinical characteristics, treatment strategies, and outcomes of COVID-19 patients with T2DM, assisting clinicians in early identification of cases likely to progress rapidly to severe or critical stages, and evaluating the effectiveness of systemic glucocorticoids in this patient population. We also investigate the incidence of long COVID-19 syndrome and interstitial pneumonia during 6-month follow-up after discharge, to provide comprehensive evidence for the clinical management and long-term prognosis assessment of these patients.

Among the 624 COVID-19 patients with T2DM included in this study, male patients constituted over 60% in both the severe and non-severe groups. Multiple studies have demonstrated that male COVID-19 patients exhibit higher rates of hospitalization, ICU admission, and mortality compared to female patients.^{12,13} Univariate and multivariate logistic regression analyses revealed that age and gender were independent risk factors for disease progression in COVID-19 patients with T2DM. This phenomenon may be attributed to the lower concentration of androgens in elderly males, which can exacerbate inflammatory responses, while estrogens in females may facilitate viral clearance.^{14,15} Multivariate logistic regression identified a prior history of cerebrovascular disease as an independent predictor of severe COVID-19 outcomes among patients with T2DM. This finding is consistent with other studies reporting that COVID-19 patients with preexisting cerebrovascular disease have poorer clinical outcomes.^{16,17}

The interplay between diabetes mellitus, hyperglycemia, and infectious diseases has been well-known in clinical practice, serving as significant predictors of disease severity in infected patients, including those with influenza A and Middle East respiratory syndrome coronavirus.¹⁸ We found that both FBG and glycosylated hemoglobin levels were elevated above normal ranges upon admission for both severe and non-severe groups, with the FBG increasing more significantly in the severe group. Univariate and multivariate logistic regression analyses revealed that elevated FBG was an independent risk factor for disease severity in COVID-19 patients with T2DM. Alahmad et al reported that patients presenting with elevated FBG had a higher likelihood of requiring ICU admission.⁴ This phenomenon may be attributed to long-term hyperglycemia in T2DM patients, which induces mitochondrial dysfunction and reactive oxygen species (ROS) generation. Excessive ROS impairs both innate and adaptive immune responses. The hyperglycemic state enhances susceptibility to bacterial infections, providing pathogens with a favorable environment to increase their virulence.^{5,6} Additionally, Pal et al highlighted that the interaction between COVID-19 and T2DM creates a vicious cycle.¹⁹ The novel coronavirus enters pancreatic β cells via angiotensin-converting enzyme 2 (ACE2) receptors, reducing insulin secretion and inducing β cell apoptosis, thereby damaging pancreatic islets and causing stress-induced hyperglycemia, which exacerbates diabetes.²⁰ Multiple studies have investigated the effects of various glucose-lowering agents on COVID-19 patients with T2DM. Metformin has been demonstrated to directly interfere with cellular energy metabolism essential for SARS-CoV-2 replication, thereby inhibiting viral proliferation and accelerating viral clearance. It also activates AMP-activated protein kinase (AMPK) and stabilizes ACE2, leading to suppression of multiple inflammatory pathways and potential mitigation of pulmonary injury.^{21,22} Furthermore, evidence from several high-quality observational studies indicates that metformin use is associated with a reduced risk of developing long COVID-19 syndrome following acute COVID-19 infection.^{23,24} Suresh et al reported that sodium-glucose cotransporter-2 inhibitors (SGLT2i) are associated with lower mortality and reduced hospitalization rates in hospitalized COVID-19 patients with T2DM.²⁵ Similarly, Yeh et al found that SGLT2i use may alleviate cognitive and pain symptoms related to long COVID in this population.²⁶ In contrast, a multicenter, open-label randomized controlled trial demonstrated that SGLT2i did not significantly improve organ support-free days or reduce mortality in hospitalized patients with COVID-19, findings consistent with those of the RECOVERY Collaborative Group.^{27,28} Notably, however, all cited studies consistently report favorable safety profiles for SGLT2i, even in critically ill, hospitalized patients at high risk of mortality or requiring organ support. Collectively, these findings underscore the importance of individualized selection of antihyperglycemic

agents in the management of COVID-19 patients with T2DM, guided by clinical factors including glucose control status, disease severity, and risk of complications.

SARS-CoV-2 frequently invades the human respiratory tract via droplet transmission and subsequently enters pulmonary epithelial cells through the ACE2 receptor. Besides pulmonary epithelial cells, ACE2 is also expressed on the cell membranes of vascular, cardiac, cerebral, and gastrointestinal tissues. As a result, patients frequently exhibit organ dysfunction consistent with our findings. Inflammatory markers in the severe group were significantly elevated compared to the non-severe group, while albumin levels and absolute counts of CD3⁺, CD4⁺, and CD8⁺ lymphocytes were markedly lower. These findings suggest that patients in the severe group exhibit impaired cellular immune function and nutritional status, more pronounced cytokine-mediated inflammatory responses, and a higher likelihood of bacterial infection, potentially due to extensive viral replication.²⁹ Research indicates that cytokine storm is a primary contributor to ARDS and multi-organ dysfunction.³⁰ Following SARS-CoV-2 infection, an influx of neutrophils and monocytes releases various pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor- α , leading to an inflammatory cascade that damages vital organs like the lungs and heart.³¹ The efficacy of glucocorticoids in mitigating non-infectious immune inflammation in COVID-19 has been well-established, and their use is recommended for severe and critical patients.^{8,32} However, the administration of glucocorticoids poses a risk of exacerbating hyperglycemia in patients with T2DM, potentially leading to further immunosuppression, impaired viral clearance, and disease progression. Batule et al demonstrated that glucocorticoids exerted a protective effect in patients with severe COVID-19 and diabetes,³³ whereas Xu et al reported that glucocorticoid treatment increased the mortality rate by threefold in patients with severe COVID-19 and T2DM compared to those not receiving glucocorticoids.³⁴ The aforementioned studies included only a limited number of patients with T2DM, leading to inconsistent findings due to small sample sizes. Our study found that, among patients with non-severe COVID-19, those receiving systemic glucocorticoids had a significantly longer hospital stay than untreated counterparts. Furthermore, a higher proportion of glucocorticoid-treated non-severe patients reported long COVID-19 syndrome following hospital discharge. In contrast, among patients requiring respiratory support, no statistically significant difference in length of hospital stay was observed between glucocorticoid-treated and untreated groups. Notably, among patients in severe group, systemic glucocorticoid administration was associated with lower mortality. Within the severe group with poor glucose control, glucocorticoid treatment remained effective.

Patients with T2DM are considered a high-risk group for long COVID-19 syndrome due to chronic metabolic disorders and a persistent inflammatory state,^{35,36} while long COVID-19 syndrome may further exacerbate blood glucose fluctuations.³⁷ The follow-up results of our study suggest that among non-severe COVID-19 patients with T2DM, the use of systemic glucocorticoids may be associated with an increased risk of long COVID-19 syndrome after discharge. This finding indicates that clinicians should strictly evaluate the necessity of systemic glucocorticoid therapy in this specific patient population. This finding indicates that clinicians need to strictly adhere to the indications for systemic glucocorticoid use in this patient population. Sanjay et al found that the use of inhaled corticosteroids in these patients can reduce exacerbation rates and improve clinical symptoms.³⁸ Local administration via inhalation is considered safer compared to systemic administration, which may offer a more favorable risk-benefit profile for milder cases.

Our study has several limitations. First, this was a retrospective cohort study with a 6-month post-discharge follow-up. Long-term outcomes including long COVID-19 syndrome and interstitial pneumonia were collected via telephone interviews or outpatient medical records, rather than being prospectively planned and recorded, which may introduce recall bias and incomplete information. Second, we were unable to obtain comprehensive medical data for some patients, and approximately one-third of patients were lost to follow-up, which may be attributed to the outpatient-based design. Third, the decision to administer glucocorticoids was based on individual physician discretion rather than a standardized protocol. Fourth, data regarding blood glucose fluctuations in patients following glucocorticoid therapy is incomplete. Fifth, due to unstable blood glucose levels in COVID-19 patients with T2DM after admission, especially those receiving glucocorticoid therapy, insulin was generally used for glucose control during hospitalization. However, as a retrospective analysis, we could not collect complete data on the glucose-lowering medications that patients routinely used before admission, which limits our ability to discuss the potential impact of different glucose-lowering agents on COVID-19-related symptoms and outcomes. Despite these limitations, we performed a comprehensive analysis of the clinical characteristics, evaluated the efficacy of glucocorticoids, and explored the long-term prognosis including long COVID-19

and interstitial pneumonia in COVID-19 patients with T2DM, which may provide evidence for clinical management. However, owing to the inherent limitations of our retrospective design, our findings should be interpreted with caution. Further well-designed, prospective cohort studies with larger sample sizes, standardized intervention protocols, and longer follow-up durations are warranted to validate our results, explore the underlying mechanisms of long-term complications, and provide more robust evidence for the clinical management of COVID-19 patients with T2DM.

Conclusion

T2DM patients with advanced age, male gender, cerebrovascular disease history, and poor FBG are at higher risk of progressing to severe or critical conditions upon SARS-CoV-2 infection. Glucose control is of importance for COVID-19 patients with T2DM. In mild or moderate cases, systemic use of glucocorticoid therapy should be strictly evaluated. In severe or critical cases, cautious, appropriate use of glucocorticoids could improve clinical outcomes.

Abbreviations

T2DM, type 2 diabetes mellitus; ICU, intensive care unit; IQRs, interquartile ranges; WBC, white blood cell count; Neu, neutrophil; Lym, lymphocyte; IL-6, interleukin-6; FBG, fasting blood glucose; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK-MB, creatine kinase isoenzyme MB; PT, prothrombin time; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; ROS, reactive oxygen species; ACE2, angiotensin-converting enzyme 2; AMPK, AMP-activated protein kinase; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, ZYH, upon reasonable request.

Ethics Approval and Informed Consent

This work was approved by the Ethical Review Committee of the First Affiliated Hospital of Guangxi Medical University (2024-E282-01) and the Peoples Hospital of Guangxi Zhuang Autonomous Region (KY-IIT-2023-107). Written informed consents were obtained from the participants.

Author Contributions

SYW and XMH: conceived the concept of this study, manuscript writing. SYW, XNL, SQL, MCW, LMH, GRC, MFW, and YN: data analysis and interpretation. ZYH: ensuring questions related to the accuracy or integrity of the work are appropriately investigated and resolved. All authors reviewed the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no competing interests to declare.

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