Clinical Research Article

Impacts of Type 2 Diabetes on Disease Severity, Therapeutic Effect, and Mortality of Patients With COVID-19

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; Cr, creatinine; CRP, C-reactive protein; CT, computed tomography; IL, interleukin; LDH, lactate dehydrogenase; MERS-CoV, Middle East respiratory syndrome coronavirus; OR, odds ratio; SARS-CoV, severe acute respiratory syndrome coronavirus; T2DM, type 2 diabetes mellitus; Th, T-helper; WHO, World Health Organization.

Abstract

Purpose: Coronavirus disease 2019 (COVID-19) has become a topic of concern worldwide; however, the impacts of type 2 diabetes mellitus (T2DM) on disease severity, therapeutic effect, and mortality of patients with COVID-19 are unclear.

Methods: All consecutive patients with COVID-19 admitted to the Renmin Hospital of Wuhan University from January 11 to February 6, 2020, were included in this study.

Results: A total of 663 patients with COVID-19 were included, while 67 patients with T2DM accounted for 10.1% of the total. Compared with patients with COVID-19 without T2DM, those with T2DM were older (aged 66 years vs 57 years; *P* < 0.001) and had a male predominance (62.7% vs 37.3%; *P* = 0.019) and higher prevalence of cardiovascular diseases (61.2% vs 20.6%; *P* < 0.001) and urinary diseases (9% vs 2.5%; *P* = 0.014). Patients with T2DM were prone to developing severe (58.2% vs 46.3%; *P* = 0.002) and critical COVID-19 (20.9% vs 13.4%; *P* = 0.002) and having poor therapeutic effect (76.1% vs 60.4%; *P* = 0.017). But there was no obvious difference in the mortality between patients with COVID-19 with and without T2DM (4.5% vs 3.7%; *P* = 0.732). Multivariate logistic regression analysis identified that T2DM was associated with poor therapeutic effect in patients with COVID-19 (odd ratio [OR] 2.99; 95% confidence interval [CI], 1.07-8.66; *P* = 0.04). Moreover, having a severe and critical COVID-19 condition (OR 3.27; 95% CI, 1.02-9.00; *P* = 0.029) and decreased lymphocytes (OR 1.59; 95% CI, 1.10-2.34; *P* = 0.016) were independent risk factors associated with poor therapeutic effect in patients with COVID-19 with T2DM.

Conclusions: T2DM influenced the disease severity and therapeutic effect and was one of the independent risk factors for poor therapeutic effect in patients with COVID-19.

Key Words: coronavirus disease 2019, type 2 diabetes mellitus, disease severity, therapeutic effect, risk factors

Coronavirus is named coronavirus because it looks like a corolla. Severe acute respiratory syndrome coronavirus (SARS-CoV) (1), Middle East respiratory syndrome coronavirus (MERS-CoV) (2), and SARS-CoV-2 (previously known as 2019-nCoV) (3) are now well known around the world. Additionally, there are coronaviruses named 229E, OC43, and human enteric coronavirus (4). Coronaviruses are single-stranded ribonucleic acids that are infectious and sensitive to ether, chloroform, 75% medical alcohol, and ultraviolet light. Currently, no drugs and vaccines can be used to efficaciously prevent it or cure patients with coronavirus.

In December 2019, the SARS-CoV-2 broke out in Wuhan, Hubei Province, China. Because the outbreak of SARS-CoV-2 was near the Chinese traditional spring festival, the virus spread from Wuhan to all parts of the country with those returning home. On January 30, 2020, the World Health Organization (WHO) announced that the SARS-CoV-2 epidemic was listed as a public health emergency of international concern. This public infectious disease has become the biggest threat to public health in China and even the world. As of June 26, 2020, a total of 9,715,530 patients with COVID-19 have been diagnosed worldwide, and 491,995 patients have died. Among the diagnosed patients in China, most were aged 30 to 79 years (86.6%); patients in Hubei Province accounted for 74.7%, and the majority of patients with COVID-19 were in mild and moderate condition, accounting for 80.9%. From the perspective of patient comorbidities, the proportion of patients with diabetes is 5.3% in China (5).

Up to 10.4% of Chinese individuals have type 2 diabetes mellitus (T2DM), and the total number of people with diabetes in China ranks first in the world and exceeds 100 million (6). Excessive fluctuations in blood glucose levels in patients with diabetes can cause glucose, fat, and protein metabolic disorders with long-term hyperglycemic conditions, which lead to a decline in the body's immune function and reduction in respiratory organ function. Thus, intrapulmonary infection is very common and prone to severe pneumonia in patients with diabetes (7). The severe stress response triggered by severe pneumonia will lead to proinflammatory and anti-inflammatory balance disorders in the body. The immense release of catecholamines and glucocorticoids induces blood glucose elevation, further aggravating the infection, leading to a vicious cycle of the disease. When it becomes severe, pneumonia is a threat for patients with diabetes (8). Severe pneumonia and diabetes induce each other; diabetes will promote the onset of pneumonia, and the patient's infection is difficult to control.

The purpose of this study was to analyze the clinical characteristics of patients with COVID-19 with T2DM and find the impacts of T2DM on disease severity, therapeutic effect, and mortality of patients with COVID-19.

Materials and Methods

Study design and patient cohort

We retrospectively analyzed the clinical characteristics of all consecutive patients diagnosed with COVID-19 admitted to the Renmin Hospital of Wuhan University from January 11 to February 6, 2020. Oral or telephone informed consent was obtained from all survival patients or the first-degree relatives of patients who had died who were enrolled in the study when we contacted patients with COVID-19 or their families for patient information. The diagnosis was based on the positive result of real-time reverse transcription polymerase chain reaction, which is the presence of SARS-CoV-2 in both the nasal and pharyngeal swab specimens. The clinical outcomes were followed up through February 9, 2020. This study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University.

We collected clinical data including basic information (age, gender, occupation), comorbidities (classified by systems), symptoms and signs, laboratory findings, chest computed tomography (CT) images, hospital stay, and primary outcomes including disease severity at admission (patient condition), therapeutic effect (improvement or no improvement), and mortality. The criteria used to define CT findings as "normal" and "abnormal" was based on interim guidelines for COVID-19 (trial implementation of the revised fifth edition) from the National Health Organization and Commission of China (9). When chest CT finding showed the following features, it was defined as normal: no enlargement of 2 hilus pulmonis; unobstructed trachea and bronchi; clear blood vessels; no enlarged lymph nodes in mediastinum; no abnormalities in pleura, ribs, and soft tissues of the chest wall; and no hydrothorax. Otherwise, chest CT images were regarded as abnormal. CT images were independently reviewed by 2 radiologists, and all discrepancies were resolved by consensus. CT images with the following features were defined as pneumonia: multiple

small, patchy shadows and interstitial changes or multiple ground-glass opacity and infiltrating shadow in the lungs. When chest CT images showed pneumonia was just on 1 side of lungs, it was defined as "single side," and when chest CT images showed bilateral pneumonia, it was defined as "double sides."

The disease severity is determined based on the interim guidelines for COVID-19 from the National Health Organization and Commission of China and the WHO ([9], [10]). According to the patient's symptoms and signs, laboratory findings, and imaging results at admission, the disease severity of patients with COVID-19 (patient condition) is classified into the following 4 types of conditions: mild, moderate, severe, and critical. Patients with mild clinical symptoms and no finding of pneumonia on chest CT image were considered as having a mild condition. If patients had a fever or respiratory symptoms, they were classified into the moderate condition. Once the patients had 1 of the following 3 symptoms, they were treated as severe: respiratory disorders and respiratory rate more than 30 times per minute, blood oxygen saturation of fingertips below 93% at rest, or partial arterial oxygen pressure/fraction of inspired oxygen ≤300 mmHg. Patients with 1 of the following 3 serious situations were considered as critical: respiratory failure requiring mechanical ventilation, state of shock, or other organ failure requiring treatment in the intensive care unit. The criteria of therapeutic effect are based on interim guidelines for COVID-19 (trial implementation of the revised fifth edition) from the National Health Organization and Commission of China ([9]). When the patient had 1 of the following conditions during follow-up, the patient's therapeutic effect was considered as improvement: (1)Body temperature returned to normal (below 37.3°C) for at least

3 days, and respiratory symptoms improved significantly (disappeared or obviously relieved); (2) gradual reduction of pulmonary inflammation according to lung CT image analysis (obviously reduced shadow area); (3)negative results in 2 consecutive tests for SARS-CoV-2 real-time reverse transcription polymerase chain reaction detection (sampling time at least 1 day apart). Otherwise, the patient's therapeutic effects were regarded as having no improvement.

Forty-six patients who had type I diabetes (1 patient), missing data (32 patients), or transferred to other hospitals (13 patients) were excluded. A total of 663 patients with COVID-19 were included in the study ([Fig. 1]). Based on whether or not the patients had T2DM (diagnostic criteria of T2DM based on Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes, 2017 Edition) ([6]), the patients were divided into the T2DM group and the non-T2DM group. The clinical characteristics of the 2 groups were compared to observe the differences between patients with COVID-19 with and without T2DM and to attain the impact of T2DM on disease severity, therapeutic effect, and mortality of patients with COVID-19.

Statistical analysis

Statistical analysis was performed using R software (version 3.4.1). The comparison of variables between those with and without T2DM was performed using the Fisher exact test or the chi-square. The risk factors associated with therapeutic effect (no improvement) were analyzed using logistic regression. All variables associated with therapeutic effect were included in the univariate regression model, and all variables with $P < 0.05$ level in univariate analyses were entered into the logistic multivariate regression models. Estimates were
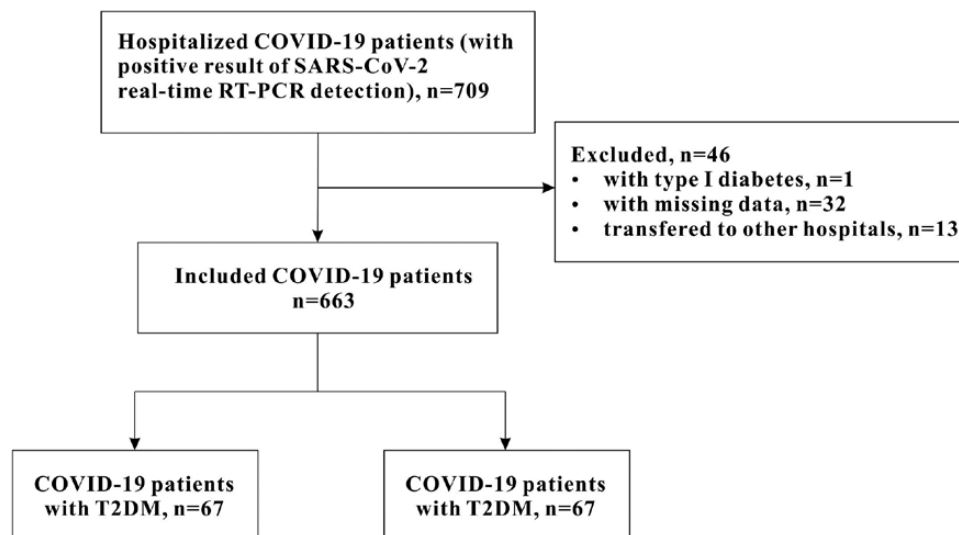

Figure 1. Flow diagram of included patients. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; RT-PCR, real-time reverse transcription polymerase chain reaction; T2DM, type 2 diabetes mellitus.

odds ratios (ORs) with their 95% confidence intervals (CI). Statistical significance was set at $P < 0.05$ (2-tailed).

Results

A total of 663 patients diagnosed with COVID-19 were included in our study (Fig. 1). Of those, 67 patients had T2DM (25 women and 42 men), which accounted for 10.1% of all patients with COVID-19. Among 67 patients with T2DM, 9 patients maintained blood glucose by subcutaneous injection of long-acting insulin (insulin glargine or insulin detemir injection) once a day at bedtime and short-acting insulin (insulin aspart or recombinant human insulin lispro injection) before each meal. Seventeen patients subcutaneously injected premixed insulin twice daily (insulin aspart 30 or isophane protamine biosynthetic human insulin premixed 30R or mixed protamine zinc recombinant human insulin lispro injection-25R/50R). Twelve patients combined premixed insulin subcutaneously injected twice daily with an alpha-glycosidase inhibitor (acarbose tablets) before lunch. Nineteen patients were administered oral metformin hydrochloride tablets and alpha glycosidase inhibitors (acarbose tablets). Ten patients were administered oral sulfonylureas (gliclazide or glimepiride tablets) combined with alpha-glycosidase inhibitors (acarbose tablets).

According to the medical records, no newly diagnosed patients with T2DM or patients with large blood glucose fluctuations were found during the whole follow-up process.

Differences in baseline characteristics between patients with and without T2DM with COVID-19

Table 1 shows the baseline characteristics in patients with COVID-19 with or without T2DM. Patients with T2DM were older than patients without T2DM (aged 66 years vs 57 years; $P < 0.001$). Of 67 patients with T2DM, there was a significant male predominance (62.7% vs 37.3% for male and female, respectively; $P = 0.019$). Most of the patients with T2DM were retired (62.7% vs 31.0%; $P < 0.001$). Additionally, patients with T2DM had more underlying diseases: higher prevalence of cardiovascular diseases (61.2% vs 20.6%; $P < 0.001$) and urinary diseases (9% vs 2.5%; $P = 0.014$).

Differences in symptoms and signs between patients with and without T2DM with COVID-19

We analyzed symptoms and signs of patients with SARS-CoV-2, and the differences between patients with COVID-19 with and without T2DM. As shown in Table 2, most

Table 1. Clinical characteristics of patients with COVID-19 with and without type 2 diabetes mellitus hospitalized in Wuhan, China

	Total (n = 663)	With T2DM (n = 67)	Without T2DM (n = 596)	P Value
Age, years, mean (IQR)	58 (44, 69)	66 (60, 74)	57 (42, 68)	<0.001
<60	348 (52.5)	16 (23.9)	332 (55.7)	
≥60	315 (47.5)	51 (76.1)	264 (44.3)	<0.001
Gender				0.019
Female	342 (51.6)	25 (37.3)	317 (53.2)	
Male	321 (48.4)	42 (62.7)	279 (46.8)	
Occupation				<0.001
Retired	227 (34.2)	42 (62.7)	185 (31.0)	
Employee	189 (28.5)	4 (6.0)	185 (31.0)	
Unemployed	30 (4.5)	2 (3.0)	28 (4.7)	
Civil servant	22 (3.3)	2 (3.0)	20 (3.4)	
Self-employed	12 (1.8)	0 (0)	12 (2.0)	
Farmer	8 (1.2)	0 (0)	8 (1.3)	
Student	3 (0.5)	0 (0)	3 (0.5)	
Others	172 (25.9)	17 (25.4)	155 (26.0)	
Comorbidities				
Respiratory diseases	51 (7.7)	7 (10.4)	44 (7.4)	0.515
Cardiovascular diseases	164 (24.7)	41 (61.2)	123 (20.6)	<0.001
Digestive diseases	31 (4.7)	6 (9.0)	25 (4.2)	0.116
Urinary diseases	21 (3.2)	6 (9.0)	15 (2.5)	0.014
Cancer	14 (2.1)	1 (1.5)	13 (2.2)	1
Immune diseases (%)	6 (0.9)	1 (1.5)	5 (0.8)	0.474

Data are n (%), n/N (%), mean (SD), and median (IQR). $P < 0.05$ was considered statistically significant.
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; SD, standard deviation; T2DM, type 2 diabetes mellitus.

patients with COVID-19 had fever (79.5%). However, there were no significant differences in symptoms and signs between patients with and without T2DM.

Differences in laboratory findings and chest CT images between patients with and without T2DM with COVID-19

Table 3 shows the results of laboratory findings and chest CT images of patients diagnosed with COVID-19 and which also analyzed the differences of patients with and without T2DM with COVID-19. Laboratory findings showed that white blood cell count (76.4%), neutrophil count (62.2%), hemoglobin (64.3%), alanine aminotransferase (ALT) (75.5%), aspartate aminotransferase (AST; 72.3%), and creatinine (Cr; 89.0%) were within normal range in most patients diagnosed with COVID-19. Most of the patients had lymphopenia (54.5%) and hypoalbuminemia (72.2%). Furthermore, lactate dehydrogenase (LDH; 51.9%) and C-reactive protein (CRP; 71.2%) were above the normal range. The neutrophil count (40.6% vs 29.4%; $P = 0.036$) was significantly more increased in patients with T2DM than in patients without T2DM. However, hemoglobin (50.0% vs 33.7%; $P = 0.009$) and albumin (82.8% vs 71.0%; $P = 0.045$) were significantly more decreased in patients with T2DM than patients without T2DM. There were no significant differences in white

blood cell count, ALT, AST, Cr, LDH, and CRP between the 2 groups. Chest CT images showed that most of the patients diagnosed with COVID-19 predominantly had bilateral pneumonia (92.6%). However, there was no significant difference in chest CT images between the T2DM and non-T2DM group.

Differences in outcomes and hospital stay between patients with and without T2DM with COVID-19

Table 4 shows the primary outcomes (including disease severity at admission, therapeutic effect, and mortality) and hospital stay of patients with and without T2DM with COVID-19. Of all patients with COVID-19, 69.1% of patient hospital stays were less than 7 days. Most of the patients were in a severe (47.55%) and a moderate (37.9%) state, while 62% of the patients had no improvement after treatment, and 3.8% of patients died. There was no significant difference in hospital stay and mortality for patients with or without T2DM. However, patients with T2DM were more likely to develop severe (58.2% vs 46.3%; $P = 0.002$) and critical COVID-19 (20.9% vs 13.4%; $P = 0.002$) than patients without T2DM. Additionally, the therapeutic effect of patients with T2DM was worse than in patients without T2DM (76.1% vs 60.4%; $P = 0.017$).

Table 2. Signs and symptoms of patients with COVID-19 with and without type 2 diabetes mellitus hospitalized in Wuhan, China

	Total (n = 663)	With T2DM (n = 67)	Without T2DM (n = 596)	*P* Value
Respiratory symptoms				
Dry cough	410 (61.8)	40 (59.7)	370 (62.1)	0.805
Expectoration	166 (25.0)	19 (28.4)	147 (24.7)	0.608
Dyspnea	161 (24.3)	14 (20.9)	147 (24.7)	0.595
Chest tightness	154 (23.2)	13 (19.4)	141 (23.7)	0.529
Digestive symptoms				
Diarrhea	71 (10.7)	6 (9.0)	65 (10.9)	0.779
Nausea	31 (4.7)	6 (9.0)	25 (4.2)	0.116
Vomiting	17 (2.6)	3 (4.5)	14 (2.3)	0.242
Bloating	8 (1.2)	1 (1.5)	7 (1.2)	0.576
Abdominal pain	5 (0.8)	0	5 (0.8)	1
Systemic symptoms				
Fever	527 (79.5)	57 (85.1)	470 (78.9)	0.301
Fatigue	208 (31.4)	26 (38.8)	182 (30.5)	0.213
Muscle aches	63 (9.5)	9 (13.4)	54 (9.1)	0.349
Dizziness	23 (3.5)	3 (4.5)	20 (3.4)	0.499
Headache	20 (3.0)	2 (3.0)	18 (3.0)	1
Neurological symptoms				
Unconsciousness	10 (1.5)	1 (1.5)	9 (1.5)	1

Data are n (%) unless specified otherwise. *P* < 0.05 was considered statistically significant.
Abbreviations: COVID-19, coronavirus disease 2019; T2DM, type 2 diabetes mellitus.

Table 3. Laboratory findings and chest CT images of patients with COVID-19 with and without type 2 diabetes mellitus hospitalized in Wuhan, China

	Total (n = 663)	With T2DM (n = 67)	Without T2DM (n = 596)	P Value
Blood routine				
White blood cell count, × 10^9 per L				0.130
<4	66 (10.7)	5 (7.8)	61 (11.0)	
4-10	473 (76.4)	47 (73.4)	426 (76.8)	
>10	80 (12.9)	12 (18.8)	68 (12.3)	
Neutrophil count, × 10^9 per L				0.036
<1.8	45 (7.3)	2 (3.1)	43 (7.7)	
1.8-6.3	385 (62.2)	36 (56.3)	349 (62.9)	
>6.3	189 (30.5)	26 (40.6)	163 (29.4)	
Lymphocyte count, × 10^9 per L				0.452
<1.1	338 (54.6)	38 (59.4)	300 (54.1)	
1.1-3.2	275 (44.4)	25 (39.1)	250 (45.0)	
>3.2	6 (1.0)	1 (1.6)	5 (0.9)	
Hemoglobin, g/L				0.009
<115	219 (35.4)	32 (50.0)	187 (33.7)	
115-150	398 (64.3)	32 (50.0)	366 (65.9)	
>150	2 (0.3)	0 (0)	2 (0.4)	
Liver function				
ALT, U/L				0.797
7-40	466 (75.5)	47 (73.4)	419 (75.8)	
>40	151 (24.5)	17 (26.6)	134 (24.2)	
AST, U/L				0.122
13-35	466 (72.3)	52 (81.2)	394 (71.2)	
>35	171 (27.7)	12 (18.8)	159 (28.8)	
LDH, U/L				0.255
100-300	297 (48.1)	26 (40.6)	271 (49.0)	
>300	320 (51.9)	38 (59.4)	282 (51.0)	
Kidney function				
Cr, μmol/L				0.542
41-73	549 (89.0)	55 (85.9)	494 (89.3)	
>73	68 (11.0)	9 (14.1)	59 (10.7)	
Infection-related biomarkers				
CRP, mg/L				0.194
0-10	157 (28.8)	13 (21.0)	144 (29.8)	
>10	388 (71.2)	49 (79.0)	339 (70.2)	
Other markers				
Albumin, g/L				0.045
<35	444 (72.2)	53 (82.8)	391 (71.0)	
35–50	170 (27.6)	11 (17.2)	159 (28.9)	
>50	1 (0.2)	0 (0)	1 (0.2)	
LDH, U/L (%)				0.255
100-300	297 (48.1)	26 (40.6)	271 (49.0)	
>300	320 (51.9)	38 (59.4)	282 (51.0)	
CT				0.846
Normal	3 (0.5)	0 (0)	3 (0.6)	
Single side	41 (6.9)	3 (5.0)	38 (7.1)	
Double side	550 (92.6)	57 (95.0)	493 (92.3)	

Data are n (%) unless specified otherwise. *P* < 0.05 was considered statistically significant.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; COVID-19, coronavirus disease 2019; Cr, creatinine; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; T2DM, type 2 diabetes mellitus.

Table 4. Outcomes of patients with COVID-19 with and without type 2 diabetes mellitus hospitalized in Wuhan, China

	Total (n = 663)	With T2DM (n = 67)	Without T2DM (n = 596)	P Value
Hospital stay				0.332
<7 days	458 (69.1)	51 (76.1)	407 (68.3)	
7-14 days	195 (29.4)	15 (22.4)	180 (30.2)	
>14 days	10 (1.5)	1 (1.5)	9 (1.5)	
Disease severity				0.002
Mild	3 (0.5)	0 (0)	3 (0.5)	
Moderate	251 (37.9)	14 (20.9)	237 (39.8)	
Severe	315 (47.5)	39 (58.2)	276 (46.3)	
Critical	94 (14.2)	14 (20.9)	80 (13.4)	
Therapeutic effect				0.017
No improvement	411 (62.0)	51 (76.1)	360 (60.4)	
Improvement	252 (38.0)	16 (23.9)	236 (39.6)	
Mortality	25 (3.8)	3 (4.5)	22 (3.7)	0.732

Data are n (%) unless specified otherwise. *P* < 0.05 was considered statistically significant.
Abbreviations: COVID-19, coronavirus disease 2019; T2DM, type 2 diabetes mellitus.

Associated risk factors for poor therapeutic effect in all patients with COVID-19 and patients with T2DM with COVID-19

In the multivariate analysis of all patients with COVID-19, being male (OR1.98; 95% CI, 1.12-3.60; *P* = 0.021), having T2DM (OR 2.99; 95% CI, 1.07-8.66; *P* = 0.04), having a severe and critical condition at admission (OR 2.34; 95% CI, 1.25-4.33; *P* = 0.007), expectoration (OR 2.14; 95% CI, 1.07-4.40; *P* = 0.034), muscle aches (OR 0.27; 95% CI, 0.11-0.64; *P* = 0.003), and albumin <35 g/L (OR 1.96; 95% CI, 1.04-3.69; *P* = 0.036) were independent risk factors associated with poor therapeutic effect. In the multivariate analysis of patients with T2DM with COVID-19, having severe and critical condition (OR 3.27; 95% CI, 1.02-9.00; *P* = 0.029) and lymphocyte count $<1.1 \times 10^9$ per L (OR 1.59; 95% CI, 1.10-2.34; *P* = 0.016) were independent risk factors associated with poor therapeutic effect (Table 5).

Discussion

We analyzed the clinical characteristics of 663 patients diagnosed with COVID-19 and found that of all 663 patients, 67 (10.1%) patients had T2DM, which is much higher than the infectious rate of patients with diabetes with COVID-19 nationwide (5.3%) (5). It is reported that among patients infected with MERS-CoV, 50% had T2DM (11). The prevalence of T2DM in China is 10.4% (6), and it is estimated that patients with T2DM will not increase the risk of infection with SARS-CoV-2. However, more multicenter data are needed to validate this point.

Patients with T2DM in our study were older (age median 66 years vs 57 years) and mainly males (62.7%). The

results of this study are consistent with those of ordinary pneumonia, which is similar to the previous study reported (12). It was more common for males (73%) with a median age of 49 years to have COVID-19 (13). The situation was the same for MERS-CoV (14). The WHO has reported that 75.5% of patients infected with MERS-CoV were male, and the median age was 54 years (interquartile range 40-65.5, range 10-93 years) (15).

Our results show that, of patients with SARS-CoV-2, patients with T2DM with cardiovascular diseases such as hypertension, coronary heart disease, and urinary diseases such as urinary infections were significantly higher than patients without T2DM. T2DM can activate the inflammatory response downstream of nuclear factor-κB and accelerate atherosclerosis. Long-term, high-glucose stimulation will lead to increased expression of endothelin-1 and its receptors, which may cause cardiovascular complications in patients with T2DM. Studies have shown that the prognosis of T2DM-related heart disease was worse than in patients without T2DM with heart disease (16). Furthermore, patients with T2DM with urinary diseases such as urinary infections are also significantly higher than those without T2DM. Patients with T2DM are prone to infections of various systems, therefore urinary system infection is one of the most common infectious diseases (17), which is also consistent with our conclusions. The main mechanisms are as follows. First, hyperglycemia is conducive to the growth and reproduction of pathogenic bacteria. Second, hyperglycemia causes cell dehydration, electrolyte disturbances, and internal environment disturbances to promote the occurrence and spread of infection. Finally, the decrease in granulocyte function and humoral and cellular immune functions also play an important role in causing urinary system infection (18).

Table 5. Logistic regression modeling evaluating risk factors for poor therapeutic effect in overall and patients with type 2 diabetes mellitus with COVID-19 hospitalized in Wuhan, China

Items	Total				T2DM			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR; 95% CI	P Value	OR; 95% CI	P Value	OR; 95% CI	P Value	OR; 95% CI	P Value
Age ≥60	4.33 (3.09, 6.14)	<0.001	1.14 (0.60, 2.16)	0.679	3.63 (1.06, 12.57)	0.039	NA	NA
Male	1.63 (1.19, 2.25)	0.002	1.98 (1.12, 3.60)	0.021	2.81 (0.90, 9.21)	0.078	NA	NA
Respiratory diseases	2.1 (1.11, 4.26)	0.03	0.87 (0.29, 2.80)	0.81	2.00 (0.31, 39.38)	0.536	NA	NA
Cardiovascular diseases	3.76 (2.46, 5.92)	<0.001	1.66 (0.82, 3.47)	0.166	1.83 (0.58, 5.81)	0.296	NA	NA
Urinary diseases	3.80 (1.27, 16.35)	0.034	1.45 (0.24, 16.50)	0.725	1.63 (0.24, 32.55)	0.667	NA	NA
T2DM	8.56 (1.85, 44.29)	0.007	2.99 (1.07, 8.66)	0.04	NA	NA	NA	NA
Severe and critical condition	8.63 (6.05, 12.42)	<0.001	2.34 (1.25, 4.33)	0.007	4.84 (3.20, 7.37)	<0.001	3.27 (1.02, 9.00)	0.029
Fever	1.66 (1.14, 2.44)	0.009	0.93 (0.45, 1.89)	0.844	0.77 (0.11, 3.53)	0.756	NA	NA
Expectoration	2.16 (1.47, 3.23)	<0.001	2.14 (1.07, 4.40)	0.034	8.18 (1.47, 153.92)	0.05	NA	NA
Dyspnea	2.62 (1.76, 4.00)	<0.001	0.84 (0.41, 1.78)	0.65	NA	NA	NA	NA
Chest tightness	2.42 (1.61, 3.69)	<0.001	1.12 (0.55, 2.32)	0.765	1.93 (0.44, 13.44)	1.93	NA	NA
Muscle aches	0.34 (0.20, 0.57)	<0.001	0.27 (0.11, 0.64)	0.003	NA	NA	NA	NA
Dizziness	4.25 (1.44, 18.15)	0.021	3.45 (0.62, 28.01)	0.205	0.71 (0.03, 19.03)	0.817	NA	NA
Neutrophil count >6.3 × 10^9 per L	2.16 (1.47, 3.22)	<0.001	0.97 (0.45, 2.12)	0.93	NA	NA	NA	NA
Lymphocyte count <1.1 × 10^9 per L	2.10 (1.22, 3.75)	0.009	0.72 (0.23, 2.35)	0.577	4.13 (2.86, 6.03)	<0.001	1.59 (1.10, 2.34)	0.016
Hemoglobin <115 g/L	1.70 (1.17, 2.40)	0.005	1.00 (0.54, 1.88)	0.997	1.97 (0.63, 6.61)	0.252	NA	NA
ALT >40 U/L	1.97 (1.31, 3.02)	0.001	1.21 (0.54, 2.73)	0.65	3.18 (0.76, 21.90)	0.175	NA	NA
AST >35 U/L	2.11 (1.42, 3.17)	<0.001	0.72 (0.32, 1.59)	0.409	1.84 (0.42, 12.96)	0.465	NA	NA
Cr >73 mmol/L	6.55 (3.01, 17.19)	<0.001	2.89 (0.93, 11.05)	0.09	NA	NA	NA	NA
Albumin <35 g/L	2.45 (1.70, 3.52)	<0.001	1.96 (1.04, 3.69)	0.036	3.18 (0.79, 12.62)	0.095	NA	NA
LDH >300 U/L	4.09 (2.88, 5.85)	<0.001	1.43 (0.75, 2.76)	0.278	3.33 (1.05, 11.40)	0.045	2.07 (0.11, 76.34)	0.626
CRP >10 mg/L	4.79 (3.24, 7.5)	<0.001	1.76 (0.90, 3.42)	0.096	3.81 (1.01, 14.44)	0.045	10.27 (0.53, 565.07)	0.15

$P < 0.05$ was considered statistically significant.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; Cr, creatinine; CRP, C-reactive protein; GFR, glomerular filtration rate; LDH, lactate dehydrogenase; OR, odds ratio; T2DM, type 2 diabetes mellitus.

The most common symptoms at admission for patients infected with SARS-CoV-2 in our study were fever (79.5%), cough (61.8%), fatigue (31.4%), and expectoration (25.0%). Additionally, the initial symptoms of some patients were diarrhea, dizziness, and fatigue. The previous research indicated that the most common clinical symptoms of patients infected with SARS-CoV were fever (99%), nonproductive cough (69%), myalgia (49%), and dyspnea (42%) (19). It is evident that the clinical manifestations of patients with SARS-CoV-2 are different among patients, and the rate of patients with fever as the onset symptom was lower than for those with SARS-CoV infection. However, there was no significant difference in clinical manifestations between patients with and without diabetes.

After patients were infected with SARS-CoV-2, patient with T2DM with COVID-19 were more likely to develop severe and critical COVID-19, and the therapeutic effect was significantly worse than in other patients, which is consistent with the findings of patients with diabetes with SARS-CoV or MERS-CoV. Multivariate analysis by Christopher et al of patients with SARS-CoV showed that mortality, intensive hospitalization, and mechanical ventilation rates of patients with diabetes with SARS-CoV increased significantly (19). The study by Khalid et al also showed that patients with diabetes with MERS-CoV had a poorer prognosis, significantly worse clinical outcomes, and a significantly increased mortality rate than other patients (20). The WHO considers diabetes as a risk factor for MERS-CoV infection (21).

Patients with T2DM with COVID-19 are prone to a severe state, and the therapeutic effects are much poorer than in patients without T2DM. The possible explanations are as follows. First, the pulmonary vascular bed and alveolar surfactants in patients with diabetes are often damaged. On autopsy results of patients with T2DM, thickening of the alveolar epithelium, pulmonary capillary basal layer, and pulmonary microangiopathy are often observed, and patients with diabetes often have significant decline in lung function (22). Second, hyperglycemia and insulin deficiency in patients with diabetes will reduce synthesis of proinflammatory factors such as interferon-γ and interleukin 15 (IL-15) and have influence on downstream acute inflammatory responses. Therefore, it will impair the host's innate and humoral immunity (22). It has been found that the inflammatory substance interleukin-1β (IL-1β) and oxidative stress marker human 8 isoprostaglandin F2α (8-iso-PGF2α) in patients with T2DM are significantly higher than in those without diabetes (23). Diabetes also impairs the function of macrophages and lymphocytes, which reduces the immune response and makes individuals more susceptible to infections (24). Third, chronic disease (such as diabetes) and infectious diseases and their complications share several common characteristics such as endothelial dysfunction, proinflammatory status, and innate immune response (25-27). When viral infection is severe, the excess of cytokines related to the conversion of T-helper type 1 (Th1) to Th2 and the cytokine synthesis disorder caused by metabolic diseases may cause damage to the endothelium and lead to a series of subsequent complications (27). Innate immune changes and the transformation of Th1 (the microbicidal effect of interferon-γ) to Th2 (anti-inflammatory IL-4, -5, -10, and -13) make the virus presentation stronger in patients with diabetes, therefore fatal allergy can be observed in virally infected patients with diabetes (28).

For male patients with T2DM, having a severe and critical condition at admission, muscle aches, expectoration, and albumin <35 g/L were independent risk factors associated with therapeutic effect (no improvement) of all patients with COVID-19. However, having a severe and critical condition and lymphocyte count $<1.1 \times 10^9$ per L were only 2 independent risk factors associated with no improvement.

The mortality rate among all patients with COVID-19 in our study was 3.8%, which is similar to the national mortality rate (3.67%), and the mortality rate of patients with T2DM with COVID-19 in our study was 4.5% (3/663). However, our study also has some shortcomings. First, there were only 3 deaths in patients with T2DM. It was impossible to make a multivariate regression analysis with mortality as the dependent variable, so we conducted multivariate regression analysis with therapeutic effect (no improvement) as the dependent variable. Second, we acknowledge the limitation that there were a number of covarying differences between control participants and the individuals with T2DM because of the individual differences in the patients. Third, there is increasing evidence supporting that obesity is one of the important risk factors for COVID-19, especially in the T2DM population. However, in this study there is an absence of data on body mass index (overweight or obese) since we did not collect enough data on body mass index or factors of being overweight and obese to analyze. And last, our study is a single-center study.

Conclusion

T2DM was associated with no improvement in patients with COVID-19. Patients with T2DM were prone to developing into severe and critical condition of COVID-19. Furthermore, having a severe and critical condition and decreased lymphocyte count were independent risk factors

that influence the improvement of patients with T2DM with COVID-19.

Additional Information

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References

1. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med.* 2003;**348**(20):1953-1966.

2. World Health Organization. Middle East Respiratory Syndrome Coronavirus (MERS-CoV). November, 2019. https://www.who.int/csr/disease/coronavirus_infections/risk-assessment-august-2018.pdf?ua=1. Accessed June 9, 2020.

3. Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. *Transfus Med Rev.* 2020;**34**(2):75-80.

4. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology.* 2018;**23**(2):130-137.

5. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2020;**41**(2):145-151.

6. Chinese Diabetes Association. Chinese guidelines for the prevention and treatment of type 2 diabetes (2017 edition). *Zhonghua Tang Niao Bing Za Zhi.* 2018;**10**(1): 4-67.

7. Venmans LM, Bont J, Gorter KJ, Verheij TJ, Rutten GE, Hak E. Prediction of complicated lower respiratory tract infections in older patients with diabetes. *Br J Gen Pract.* 2008;**58**(553):564-568.

8. Klekotka RB, Mizgała E, Król W. The etiology of lower respiratory tract infections in people with diabetes. *Pneumonol Alergol Pol.* 2015;**83**(5):401-408.

9. National Health Organization and Commission of China. Interim Guidelines for COVID-19 (Trial Implementation of Revised Fifth Edition). http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcaf1e3e13a/files/ab6bec7f93e64e7f998d802991203cd6.pdf. Accessed February 8, 2020.

10. World Health Organization. Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (2019-nCoV) Infection is Suspected: Interim Guidance. https://apps.who.int/iris/bitstream/handle/10665/330893/WHO-nCoV-Clinical-2020.3-eng.pdf?sequence51&isAllowed5y. Accessed 28 January 2020.

11. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis.* 2016;**49**: 129-133.

12. López-de-Andrés A, Perez-Farinos N, Miguel-Díez J, et al. Type 2 diabetes and postoperative pneumonia: an observational, population based study using the Spanish Hospital Discharge Database, 2001-2015. *PLoS One.* 2019;**14** (2): e0211230.

13. Huang CL, Wang YM, Li XW, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;**395**(10223):497-506.

14. The WHO MERS-CoV Research Group. State of knowledge and data gaps of Middle East respiratory syndrome coronavirus (MERS-CoV) in humans. *PLOS Currents Outbreaks.* 2013;**5**:ecurrents.

15. World Health Organization. WHO MERS-CoV Global Summary and Assessment of Risk. https://www.who.int/emergencies/mers-cov/risk-assessment-july-2017.pdf?ua=1. Accessed July 21, 2017.

16. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res.* 2018;**122**(4):624-638.

17. Korbel L, Spencer JD. Diabetes mellitus and infection: an evaluation of hospital utilization and management costs in the United States. *J Diabetes Complicat.* 2015;**29**(2):192-195.

18. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. *Diabetes Care.* 2018;**41**(3):513-521.

19. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA.* 2003;**289**(21): 2801-2809.

20. Alanazi KH, Abedi GR, Midgley CM, et al. Diabetes mellitus, hypertension, and death among 32 patients with MERS-CoV infection, Saudi Arabia. *Emerg Infect Dis.* 2020;**26**(1):166-168.

21. Visca D, Pignatti P, Spanevello A, Lucini E, La Rocca E. Relationship between diabetes and respiratory diseases-clinical and therapeutic aspects. *Pharmacol Res.* 2018;**137**: 230-235.

22. Odegaard JI, Chawla A. Connecting type 1 and type 2 diabetes through innate immunity. *Cold Spring Harb Perspect Med.* 2012;**2**(3):a007724.

23. Pouvreau C, Dayre A, Butkowski EG, de Jong B, Jelinek HF. Inflammation and oxidative stress markers in diabetes and hypertension. *J Inflamm Res.* 2018;**11**:61-68.

24. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis.* 2009;**9**(12):737-746.

25. Htun NS, Odermatt P, Eze IC, Boillat-Blanco N, D'Acremont V, Probst-Hensch N. Is diabetes a risk factor for a severe clinical presentation of dengue?–review and meta-analysis. *PLoS Negl Trop Dis*. 2015;**9**(4):e0003741.

26. Limonta D, Torres G, Capo V, Guzman MG. Apoptosis, vascular leakage and increased risk of severe dengue in a type 2 diabetes mellitus patient. *Diab Vasc Dis Res*. 2008;**5**(3):213-214.

27. Dharmashankar K, Widlansky ME. Vascular endothelial function and hypertension: insights and directions. *Curr Hypertens Rep*. 2010;**12**(6):448-455.

28. Toledo J, George L, Martinez E, et al. Relevance of noncommunicable comorbidities for the development of the severe forms of dengue: a systematic literature review. *PLoS Negl Trop Dis*. 2016;**10**(1):e0004284.