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CLINICAL CHARACTERISTICS OF 28 PATIENTS WITH DIABETES AND COVID-19 IN WUHAN, CHINA

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ABSTRACT

Objective: Previous studies on coronavirus disease 2019 (COVID-19) were based on information from the general population. We aimed to further clarify the clinical characteristics of diabetes with COVID-19.

Methods: Twenty-eight patients with diabetes and COVID-19 were enrolled from January 29, 2020, to February 10, 2020, with a final follow-up on February 22, 2020. Epidemiologic, demographic, clinical, laboratory, treatment, and outcome data were analyzed.

Results: The average age of the 28 patients was 68.6 ± 9.0 years. Most (75%) patients were male. Only 39.3% of the patients had a clear exposure of COVID-19. Fever (92.9%), dry cough (82.1%), and fatigue (64.3%) were the most common symptoms, followed by dyspnea (57.1%), anorexia (57.1%), diarrhea (42.9%), expectoration (25.0%), and nausea (21.4%). Fourteen patients were admitted to the intensive care unit (ICU). The hemoglobin A1c level was similar between ICU and non-ICU patients. ICU patients had a higher respiratory rate, higher levels of random blood glucose, aspartate transaminase, bilirubin, creatine, N-terminal prohormone of brain natriuretic

peptide, troponin I, D-dimers, procalcitonin, C-reactive protein, ferritin, interleukin (IL)-2R, IL-6, and IL-8 than non-ICU patients. Eleven of 14 ICU patients received noninvasive ventilation and 7 patients received invasive mechanical ventilation. Twelve patients died in the ICU group and no patients died in the non-ICU group.

Conclusion: ICU cases showed higher rates of organ failure and mortality than non-ICU cases. The poor outcomes of patients with diabetes and COVID-19 indicated that more supervision is required in these patients. (*Endocr Pract.* 2020;26:668-674)

Abbreviations:

COVID-19 = coronavirus disease 2019; **ICU** = intensive care unit; **MERS-CoV** = middle East respiratory syndrome-related coronavirus; **2019-nCoV** = 2019 novel coronavirus; **NT-proBNP** = N-terminal prohormone of brain natriuretic peptide; **SARS-CoV** = severe acute respiratory syndrome-related coronavirus

INTRODUCTION

Coronavirus disease 2019 (COVID-19) (1,2) is now rapidly spreading all over the world. It is caused by the 2019 novel coronavirus (2019nCoV) and can spread quickly from person to person (3). With increasing numbers of cases of COVID-19 globally, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on March 11, 2020. A series of studies have reported the epidemiologic and clinical characteristics of patients with COVID-19. Clinical features of COVID-19 include fever, dry cough, fatigue, normal or reduced white blood cell count, and imaging evidence of viral pneumonia. Some patients had rapid organ dysfunction, including acute respiratory distress syndrome leading to death (4). It has been reported that compared with non-intensive care

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unit (ICU) patients, ICU patients have a higher proportion of diabetes (5). It is suggested that diabetes may affect the clinical manifestations and disease progression of patients. In order to clarify the clinical characteristics of diabetes combined with COVID-19, we retrospectively collected and analyzed detailed clinical data of patients with diabetes and confirmed COVID-19, described their clinical characteristics, and compared clinical characteristics of patients with ICU care with those without ICU care.

METHODS

Study Design and Participants

For this retrospective study, 28 patients with diabetes and confirmed COVID-19 admitted to our hospital were enrolled. Our hospital is responsible for the treatments of COVID-19 assigned by the government. Patients were hospitalized from January 29, 2020, to February 10, 2020, with a final follow-up for this study on February 22, 2020. All COVID-19 patients enrolled in this study were diagnosed according to the New Coronavirus Pneumonia Prevention and Control Program (fifth edition) published by the National Health Commission of China (6). Diagnostic criteria for confirmed COVID-19 cases included 1 of the following: (1), detection of high homology of the novel coronavirus by real-time reverse transcriptase polymerase chain reaction of respiratory tract specimens or blood specimens, or (2), viral gene sequencing of respiratory specimens or blood specimens found to be highly homologous to known novel coronaviruses.

The current study was approved by the local ethical committee and written informed consent was obtained from each patient that was included.

Data Collection

Epidemiologic, demographic, clinical, laboratory, radiologic, treatment, and outcome data were obtained from patients' electronic medical records. All information was collected and managed with a data collection form. To ensure the accuracy of the data, 2 researchers (YYL and ZSJ) checked the data independently.

We collected nasopharyngeal swab samples from the upper airways of all patients. Samples were sent to the Department of Clinical Laboratory and tested for the 2019 novel coronavirus (2019-nCoV) ribonucleic acid using a kit recommended by the Chinese Center for Disease Control and Prevention. A diabetes diagnosis was confirmed according to past medical history and the demand for glucose lowering therapy. Patients who needed ventilation support or developed organ dysfunction were transferred into the ICU.

Statistical Analysis

The Shapiro-Wilk test was used to determine whether the data were normally distributed. Continuous variables

were expressed as the mean \pm SD for data of normal distribution, and as the median and interquartile range for data of non-normal distribution. Normal distribution data were subjected to a Student's *t* test, otherwise, the Mann Whitney *U* test was used. $P < .05$ was considered to be statistically significant. The Fisher exact test was used for categorical variables.

RESULTS

The study included 28 patients with diabetes and confirmed COVID-19, including 14 patients in the isolation ward and 14 patients in the ICU ward. A total of 11 (39.3%) patients had a history of exposure to confirmed COVID-19 patients (Table 1). Most (75%) patients were male. The age range of the patients was 53 to 82 years and the average age was 68.6 years. Seventeen (60.7%) patients had coexisting chronic diseases, including hypertension, heart disease, cerebrovascular disease, and chronic respiratory disease (Table 2).

The most common symptoms were fever (26 cases, 92.9%), dry cough (23 cases, 82.1%), and fatigue (18 cases, 64.3%), followed by dyspnea (16 cases, 57.1%), anorexia (16 cases, 57.1%), diarrhea (12 cases, 42.9%), and other symptoms included expectoration, pectoralgia, headache, nausea, and vomiting (Table 2). There was no significant difference in symptoms between ICU and non-ICU patients. In terms of vital signs, there were no differences in diastolic pressure, temperature on admission, and maximum temperature between the ICU group and the non-ICU group (Table 1). The heart rate and systolic pressure of ICU patients were relatively higher than those of non-ICU patients, but the difference was not statistically significant. Respiratory rate was significantly higher in ICU patients ($P < .01$).

Leukocytes (white blood cells and neutrophils) were normal or decreased in non-ICU patients but increased in ICU patients. In both ICU and non-ICU patients, lymphocytes were reduced, and hemoglobin and platelets were in the normal range (Table 3). ICU patients had higher serum levels of aspartate transaminase, total bilirubin, creatine, lactic dehydrogenase, and creatine kinase, and lower albumin levels. In terms of cardiac damage, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and troponin I were significantly increased in ICU patients. Serum levels of D-dimer were mildly elevated in non-ICU patients on admission, but significantly increased in ICU patients. Regarding the infection index, procalcitonin, C-reactive protein, ferritin, and cytokines (including interleukin (IL)-2 receptor, IL-6, and IL-8) (Table 4) were increased in both ICU patients and non-ICU patients, but more significantly increased in ICU patients. There was no significant difference in hemoglobin A1c between ICU and non-ICU patients, but random blood glucose concentrations were higher in ICU patients.

All patients received a chest computed tomography (CT) scan. Most patients showed bilateral pneumonia. Figure 1 shows the chest CT manifestations of 2 patients. All patients received antiviral therapy (oseltamivir, or arbidol, or both, 28 patients [100%]), and most of the patients received antibacterial therapy (27 patients [96.4%]). Fifty percent of non-ICU patients and 100% of ICU patients received glucocorticoid therapy. Patients with respiratory failure received insulin-based antidiabetic therapy. Patients without respiratory failure received an oral drug-based antidiabetic therapy such as metformin, sulfonylurea, α -glucosidase inhibitor, and dipeptidyl peptidase-4. Respiratory failure occurred in 5 non-ICU patients and all ICU patients. None of the non-ICU patients received noninvasive ventilation. Eleven of the 14 ICU patients received noninvasive ventilation, later 4 of them and another 3 patients received invasive mechanical ventilation. Until the final follow-up, in the ICU group, 12 patients died, and 2 patients were still in therapy. In the non-ICU group, 12 patients were discharged and 2 patients were still in therapy. In total, 42.9% of patients had fatal outcomes (Table 1).

Of these patients, 7 patients died of respiration and circulation failure, 3 patients died of multiple organ dysfunction syndrome, and 2 patients died of sudden death.

DISCUSSION

This case series provides information on the clinical characteristics of patients with diabetes and COVID-19 in Wuhan, China. As first-line doctors, we obtained detailed clinical data of the patients included. More importantly, we observed the outcomes of almost all selected patients.

The 2019nCoV is the seventh known coronavirus that can infect humans, and the remaining 6 are human coronavirus (HCoV)-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome-related coronavirus (SARS-CoV), and middle East respiratory syndrome-related coronavirus (MERS-CoV) (7). The 2 highly pathogenic viruses, SARS-CoV and MERS-CoV, cause severe respiratory syndrome in humans and the other 4 human coronaviruses induce mild upper respiratory disease. Similar to SARS-CoV and MERS-CoV, the

	Total (N = 28)	non-ICU (N = 14)	ICU (N = 14)	P value
Age (mean \pm SD)	68.6 \pm 9.0	65.8 \pm 9.4	71.4 \pm 7.9	.0974
Sex				
Male	21 (75.0)	11 (78.6)	10 (71.4)	1.0
Female	7 (25.0)	3 (21.4)	4 (28.6)	
Exposure of disease	11 (39.3)	7 (50.0)	4 (28.6)	.440
Maximum temperature	38.5 \pm 0.8	38.4 \pm 0.9	38.6 \pm 0.7	.6746
Temperature	36.7 (36.4, 38.3)	36.8 (36.4, 38.3)	36.7 (36.4, 38.2)	.8648
Respiratory rate	25 \pm 6	21 \pm 2	29 \pm 6	.0003
Heart rate	95 \pm 16	93 \pm 16	97 \pm 16	.4667
Systolic pressure	140 \pm 28	132 \pm 24	149 \pm 31	.1251
Diastolic pressure	80 \pm 13	80 \pm 13	80 \pm 13	.9555
Respiratory failure	19 (67.9)	5 (35.7)	14 (100)	.001
Nonventilator ^b	5 (26.3)	5 (100)	0 (0)	
Noninvasive ventilation ^c	11 (39.3)	0 (0)	11 (78.6)	.000
Invasive mechanical ventilation	7 (25.0)	0 (0)	7 (50.0) ^a	.006
Fatal outcome	12 (42.9)	0 (0)	12 (85.7)	.000
Respiration and circulation failure			7 (58.3)	
MODS			3 (27.3)	
Sudden death			2 (18.2)	

Abbreviations: ICU = intensive care unit; MODS = multiple organ dysfunction syndrome; 2019-nCoV = 2019 novel coronavirus.
^aFour patients were supported with noninvasive ventilation first. ^bNonventilator includes low-flow nasal cannula or face mask. ^cNoninvasive ventilation includes bilevel positive airway pressure ventilation or high-flow nasal cannula oxygen therapy.
P < .05 was considered statistically significant.

Table 2
The Comorbidities and Symptoms in Non-ICU and ICU Patients with DM

	Total (N = 28)	non-ICU (N = 14)	ICU (N = 14)	P value
Comorbidities	17 (60.7)	7 (50.0)	10 (71.4)	.440
Hypertension	15 (53.6)	5 (35.7)	10 (71.4)	.128
Cardiovascular disease	4 (14.3)	0 (0)	4 (28.6)	.098
Cerebrovascular disease	4 (14.3)	2 (14.3)	2 (14.3)	1.0
Chronic kidney disease	0 (0)	0 (0)	0 (0)	1.0
Chronic pulmonary disease	2 (14.3)	1 (7.1)	1 (7.1)	1.0
Chronic liver disease	0 (0)	0 (0)	0 (0)	1.0
Symptoms				
Fever	26 (92.9)	12 (85.7)	14 (100)	.481
Cough	23 (82.1)	11 (78.6)	12 (85.7)	1.0
Expectoration	7 (25.0)	4 (28.6)	3 (21.4)	1.0
Dyspnea	16 (57.1)	5 (35.7)	11 (78.6)	.054
Pectoralgia	3 (10.7)	3 (21.4)	0 (0)	.222
Diarrhea	12 (42.9)	8 (57.1)	4 (28.6)	.252
Nausea	6 (21.4)	4 (28.6)	2 (14.3)	.648
Vomiting	3 (10.7)	2 (14.3)	1 (7.1)	.314
Anorexia	16 (57.1)	8 (57.1)	9 (64.3)	1.0
Headache	3 (10.7)	1 (7.1)	2 (20)	1.0
Fatigue	18 (64.3)	8 (57.1)	10 (71.4)	.695

Abbreviations: DM = diabetes mellitus; ICU = intensive care unit.
P values indicate differences between non-ICU and ICU patients with DM. $P < .05$ was considered statistically significant.

ongoing outbreak of COVID-19 has been declared by the WHO as a global public health emergency. Several studies have reported the clinical characteristics of COVID-19 (1,8,9). According to our study, the symptoms of COVID-19 patients with diabetes were similar to the general population as previously reported; the most common symptoms were fever, cough, and fatigue (1). Gastrointestinal symptoms were common in patients with middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), but less common in COVID-19 patients. Diarrhea occurred in about 20 to 26% of patients with MERS-CoV or SARS-CoV infection (10,11). In the current study, 42.9% of COVID-19 patients with diabetes had diarrhea and 21.4% had nausea. This may be due to the presence of autonomic neuropathy and abnormal secretion of gastrointestinal hormones in diabetic patients, resulting in gastrointestinal dysfunction under stress. Laboratory tests also indicated that non-ICU cases with diabetes showed a similar pattern of laboratory characteristics to the general population. For example, patients had decreased lymphocyte counts, normal procalcitonin, elevated C-reactive protein, lactate dehydrogenase, and erythrocyte sedimentation rate (1,5).

There were numerous differences in laboratory findings between ICU and non-ICU cases in our study. Two of the indicators significantly increased in ICU patients were NT-proBNP and troponin I. It is reported that the infection of 2019-nCoV may cause fulminant myocarditis (12,13). The abnormalities of NT-proBNP and troponin I in ICU patients may suggest that there was a higher preponderance of heart injury in patients who were admitted to the ICU. Our observation that part of the ICU patients died of sudden death also supported this conclusion. Inflammatory indicators were also significantly increased in ICU patients. SARS-CoV and MERS-CoV infection were reported to induce increased concentrations of cytokines, and the cytokine storm was associated with pulmonary inflammation and extensive lung damage (14,15). In the current study, patients requiring ICU admission had significant higher levels of cytokines, C-reactive protein, and ferritin. Additionally, increased levels of neutrophils and procalcitonin were also observed in ICU patients. These observations suggest that a cytokine storm and secondary infections were associated with disease severity.

Recent studies indicate that the 2019-nCoV is more likely to infect older adult males with chronic comorbidities.

ties (1,4,5). The rates of diabetes in ICU and non-ICU cases were 22.2% and 5.9%, respectively (5). This indicates that 2019-nCoV pneumonia with diabetes is more likely to develop into a severe case. In total, 42.9% of patients in our study had a fatal outcome. According to a recent study, the estimated mortality rate of COVID-19 would be 5.6% for China and 15.2% outside of China (16). In-hospital mortality was even much higher (28%), as reported by Fei Zhou et al (17). Another summary report from the Chinese Center for Disease Control showed an overall fatality rate of 2.3% in patients with COVID-19 (18). Regarding other respiratory viruses, the mortality rate was about 9.6% in SARS, 38% in MERS (19) and 17.7% in H1N1 swine flu (20). It is known that people with diabetes are generally more susceptible to infections (21). Moreover, some studies identified diabetes as an independent risk factor for infection-related mortality (22,23). Diabetes has been reported to increase the risk of severe outcomes from H1N1 influenza, SARS-CoV, and MERS-CoV infection (23-26). Recently, a report by Wu et al (18) showed that the presence of diabetes increases the risk of poor outcomes for

patients with COVID-19 (18). Consistently, we observed high rates of mechanical ventilation and fatal outcomes in COVID-19 patients with diabetes. One underlying mechanism linking diabetes with disease severity was immune imbalance. Immunologic defects, such as decreased neutrophilic migration, phagocytosis, intracellular killing, and chemotaxis, cause some infections to be more frequent and severe in diabetic cases (27). Hyperglycemia was also reported to be a risk factor for mortality (25). In support of this view, we observed that the random blood glucose concentrations were much higher in ICU patients.

Limitations

There are several limitations in this study. First, the sample size was relatively small because we ruled out clinically diagnosed COVID-19 cases; the duration of collecting data was also short. Second, because our hospital is the designated hospital for severe cases, it may lead to the high mortality rate observed in the study. Third, retrospective research itself has many disadvantages. Finally, the current study is a descriptive study. Lack of a control group makes

Table 3
The Biochemical Values in Diabetics Infected with 2019-nCoV on Admission to Hospital

	Normal range	non-ICU (N = 14)	ICU (N = 14)	P value
Glycemic index				
RBG, mmol/L		9.8 ± 3.4	13.7 ± 5.1	.0273
HbA1c, %	4-6	7.5 ± 1.2	7.3 ± 0.90	.6699
Hematologic index				
WBC, 10 ⁹ /L	3.5-9.5	5.9 ± 2.0	13.1 ± 6.6	.0007
NEU, 10 ⁹ /L	1.8-6.3	4.6 ± 2.1	12.0 ± 6.6	.001
LYM, 10 ⁹ /L	1.1-3.2	0.82 (0.63, 1.09)	0.47 (0.31, 0.77)	.0345
HGB, g/L	115-150	130.0 (127.5, 140.8)	135.5 (119.8, 148.3)	.5494
PLT, 10 ⁹ /L	125-350	186.9 ± 79.3	174.8 ± 90.97	.7112
PT, seconds	11.5-14.5	14.1 (13.7, 14.6)	14.5 (13.5, 17.5)	.3818
APTT, seconds	29-42	40.7 ± 7.5	39.0 ± 4.6	.4698
D-D, µg/mL FEU	<0.5	0.8 (0.3, 1.4)	11.3 (2.6, 21.0)	.0002
Hepatic index				
ALT, U/L	≤33	17.5 (10.8, 26.0)	21 (15.5, 40.5)	.2317
AST, U/L	≤32	22.2 ± 7.2	44.8 ± 20.8	.0058
Alb, U/L	35-52	35.8 (30.7, 38.5)	31.6 (27.1, 32.7)	.0108
TBil, µmol/L	≤21	9.1 ± 3.6	15.8 ± 6.8	.0082
CK, U/L	≤170	84.5 ± 41.18	220.4 ± 128.3	.0183
LDH, U/L	135-214	256.0 (232.0, 286.5)	497.5 (428.0, 867.8)	<.0001

Abbreviations: Alb = albumin; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CK = creatine kinase; D-D = D-dimer; FEU = fibrinogen equivalent units; HbA1c = hemoglobin A1c; HGB = hemoglobin; ICU = intensive care unit; LDH = lactate dehydrogenase; LYM = lymphocytes; 2019-nCoV = 2019 novel coronavirus; NEU = neutrophils; PLT = platelets; PT = prothrombin time; RBG = random blood glucose; TBil = total bilirubin; WBC = white blood cell.
P<.05 was considered statistically significant.

Table 4 The Biochemical Values in Diabetics Infected with 2019-nCoV on Admission to Hospital				
	Normal range	non-ICU (N = 14)	ICU (N = 14)	P value
Renal index				
Urea, mmol/L	3.1-8.8	5.0 (3.0, 5.5)	9.2 (7.2, 11.3)	.0007
Cr, μmol/L	45-84	74.0 (56.0, 89.3)	85.5 (62.3, 96.8)	.2905
Inflammatory index				
CRP, mg/L	<1	12.9 (3.5, 55.7)	134.6 (73.2, 164.1)	.0004
ESR, mm/hour	0-20	28.6 ± 24.0	36.9 ± 23.6	.4199
PCT, ng/mL	0.02-0.05	0.03 (0.03, 0.06)	0.31 (0.1, 3.08)	.0006
Ferritin, μg/L	15-150	555.2 (375.6, 767.8)	1,612.0 (1,246.0, 2,290.0)	.0012
IL-2R, U/mL	223-710	677 (496, 1,016)	1,538 (1,214, 1,937)	<.0001
IL-6, pg/mL	<7.0	13.0 (2.4, 39.8)	124.5 (65.1, 199.9)	.001
IL-8, pg/mL	<62	11.0 (6.8, 21.8)	49.1 (25.2, 92.4)	.0012
IL-10, pg/mL	<9.1	5.2 (5, 7.5)	14.9 (5.9, 18.6)	.0057
TNFα, pg/mL	<8.1	9.1 (6.1, 11.0)	17.1 (8.4, 20.2)	.0559
Cardiac index				
NTproBNP, pg/mL	<285	92 (63, 658)	913 (506, 2,552)	.0031
cTnI, pg/mL	≤15.6	4.8 (2.1, 7.3)	57.6 (19.2, 239.4)	.0023

Abbreviations: Cr = creatinine; CRP = C-reactive protein; cTnI = cardiac troponin I; DM = diabetes mellitus; ESR = erythrocyte sedimentation rate; ICU = intensive care unit; IL-2R = interleukin 2 receptor; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-10 = interleukin 10; 2019-nCoV = 2019 novel coronavirus; NTproBNP = N-terminal prohormone of brain natriuretic peptide; PCT = procalcitonin; TNFα = tumor necrosis factor alpha. P values indicate differences between non-ICU and ICU patients with DM. P<.05 was considered statistically significant.

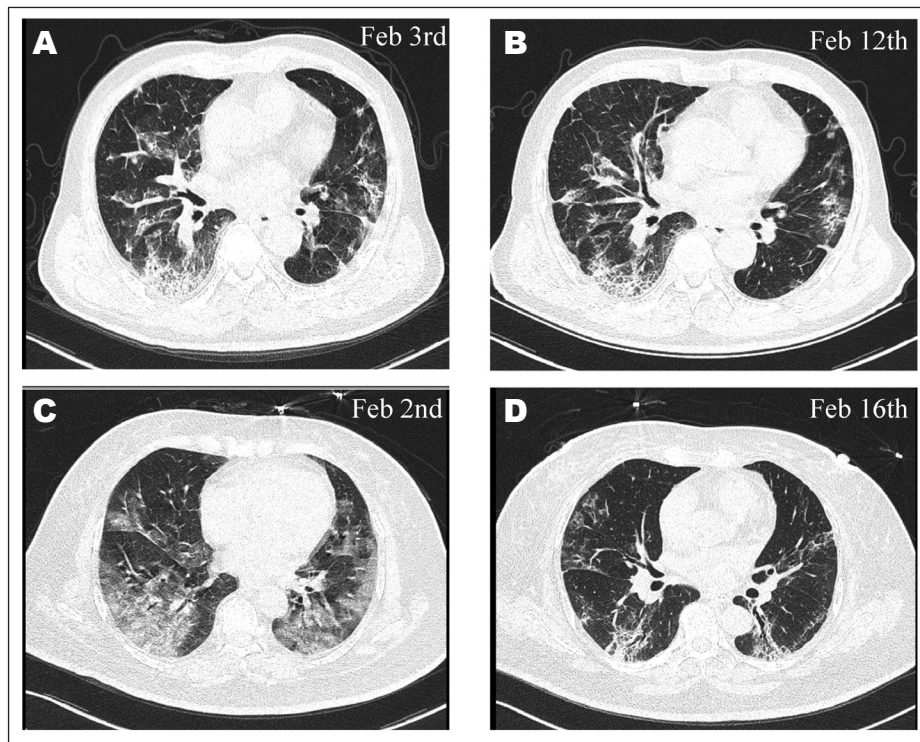


Fig. 1. A and B, indicate the lung CT of a discharged non-ICU patient. C and D, indicate the lung CT of an improving non-ICU patient. CT = computed tomography; ICU = intensive care unit.

it difficult to interpret the effect of diabetes in COVID-19. We next need to compare the clinical characteristics of COVID-19 patients with diabetes and those without diabetes, to explore the effect of diabetes on COVID-19.

CONCLUSION

Here we describe the clinical features of COVID-19 patients with diabetes and compared the features between ICU cases and non-ICU cases. ICU cases showed higher rates of organ failure and mortality than non-ICU cases. The high mortality in severe COVID-19 patients with diabetes indicated that we need more supervision in these patients.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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