Diabetes Patients of COVID-19 Infection Treated with Convalescent Plasma Transfusion in Wuhan, China

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Abstract

Background: The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 had spread all over the world, causing public health emergency. Although the diagnosis for COVID-19 such as nucleic acid test and antibody detection have been well defined, there is still a big gap of knowledge regarding for COVID-19 patients receiving convalescent plasma transfusion (CPT) therapy, especially patients with comorbidity of diabetes.

Method: In this study, out of 3059 COVID-19 patients admitted in Wuhan Huoshenshan Hospital of China, we described the characteristics of 39 diabetes patients receiving the transfusion of ABO-compatible convalescent plasma, and compared the baseline information and clinical outcome with that of 328 diabetes patients receiving traditional treatment.

Results: It was found that the intervention of CPT therapy was effective and beneficial for COVID-19 patients, including severe or critical patients with comorbidity of diabetes, without obvious adverse effects observing during the treatments. The CPT therapy significantly improved the clinical outcome of diabetes patients with COVID-19 infection, especially the duration based on six categories compared to the patients with traditional therapy.

Conclusions: This study not only provided a better understanding of COVID-19 in diabetes people receiving CPT, but also highlighted the CPT therapy was helpful for COVID-19 patients with comorbidity of diabetes.

Background

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has developed into an unprecedented global health crisis [1]. As of 1 July, 2020, the World Health Organization (WHO) has been informed of 10,357,662 confirmed cases of COVID-19, with 508,055 deaths (4.91%) documented worldwide. As part of the international joint effort, scientists and clinicians all over the world had launched unprecedented strength and complied massive data that gave the best available picture of COVID-19 [2, 3]. At present, the diagnosis for COVID-19 such as nucleic acid test and antibody detection have been well defined, whereas therapeutic strategy is rather limited. The current therapeutic strategies for COVID-19 infection mainly include anti-viral treatments, steroids, and traditional Chinese medicine, as well as oxygen therapy [4]. These treatments might beneficial for mild COVID-19 patients, but not satisfied for severe or critical patients, which account for approximately 15% of all cases [5]. In recently, the Diabetes/Metabolism Research and Reviews had published a study by Guo et al, reporting that diabetes significantly increased the risk of COVID-19 progression, and described a mortality rate of 16% among COVID-19 patients with diabetes morbidity [6]. Although various therapies are under investigation at present, there are still no specific therapeutic drugs or vaccines that could effectively eliminate the COVID-19, especially for diabetes patients and other comorbidities with COVID-19 infection

[7, 8]. To this end, it was urgently needed to develop novel treatments for severe or critical patients to cure COVID-19 and reduced the mortality, especially patients with comorbidity of diabetes.

Convalescent plasma transfusion (CPT) therapy is the administration of plasma from patients who recovered from virus infection, which was recommended as an empirical treatment during the outbreaks of Ebola virus in 2014 [9]. As a protocol for treatment of Middle East respiratory syndrome (MERS), CPT therapy was established in 2015. Apart from above diseases, CPT therapy was also suggested as effective approach for other viral infections, including SARS-CoV [10, 11], H5N1 avian influenza [12], and H1N1 influenza [13]. Especially, it was found that CPT therapy could reduce the viral burden and improve the clinical outcome without obvious side-effects during the treatment processes [14]. According to these previous experiences, it raised the hypothesis that the usage of convalescent plasma could be beneficial for patients infected with COVID-19, including severe or critical patients with comorbidity of diabetes [15].

Therefore, in this study, we described the characteristics of 39 diabetes cases out of 163 COVID-19 patients, receiving CPT therapy in Wuhan Huoshenshan Hospital of China, and compared the baseline characteristics and clinical outcome with that of COVID-19 patients with comorbidity of diabetes receiving traditional treatments. Our findings indicated that CPT therapy was effective for improving the clinical outcome of diabetes patients infected with COVID-19, including severe or critical COVID-19 patients, and with no obvious adverse effects during treatments.

Materials And Methods

Data collection

A total of 3059 patients of COVID-19 infection admitted in Wuhan Huoshenshan Hospital of China from February 4 to April 12, 2020, in which 163 COVID-19 patients had received CPT therapy. Besides, compared to 328 COVID-19 patients with comorbidity of diabetes received traditional treatment, 39 diabetes patients received CPT therapy. The severity degree of each patient was determined according to the clinical classification criterion of Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission (7th trial version) in China released on March 3, 2020 [16]. Information of clinical characteristics and laboratory findings of all patients was extracted from the hospital electronic medical records. This study was approved by the Medical Ethical Committee of Wuhan Huoshenshan Hospital of China, and written informed consent was obtained from each patient.

Donors And Cpt

The convalescent plasma was collected from patients recovered from COVID-19 infection. The ages of donors ranged between 18–55 years old, and the bodyweight was at least 45 kg for females, 50 kg for males. All donors gave written informed consent. To avoid infectious risks, the convalescent plasma was detected with serological and nucleic acid tests of hepatitis B virus, hepatitis C virus and HIV, and two times of serological tests of syphilis antibodies. As a routine check with plasma donation, the

convalescent plasma was also confirmed free of SARS-CoV-2 by real-time PCR method. Then, according to the clinical status and body weight of each recipient, ABO-compatible convalescent plasma was transfused (once with 200 mL) as soon as the plasma was available, in accordance with New Coronavirus Pneumonia Convalescent Plasma Therapy Guidance of China (7th trial version). The convalescent plasma was slow transfused for fifteen minutes in the beginning, with closely monitoring for adverse blood transfusion reactions.

Results

Characteristics of diabetes patients with COVID-19 infection

A total of 3059 patients (Ages ranged from 11 to 100 years old, mean age was 58 years old) with COVID-19 infection admitted in Wuhan Huoshenshan Hospital from February 4 to April 12, 2020. Except for 163 COVID-19 patients received CPT therapy, a total of 328 diabetes patients (Ages ranged from 33 to 90 years old, mean age was 64 years old) people out of 2893 illness received traditional treatment had comorbidity of diabetes as well, including 12 of died cases, the mortality rate was 3.66%. A total of 21 COVID-19 patients with diabetes were treated in ICU (intensive care unit) and noticed of critical illness. According to the clinical classification criterion in Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission (7th trial version), except 7 patients without severity degree, the other 321 diabetes patients of COVID-19 infection received traditional treatment were divided into three classification, including 135 (42.06%) of mild patients, 164 (51.09%) of severe patients, and 22 (6.85%) of critical patients. The hospitalization time of 328 COVID-19 patients with comorbidity of diabetes ranged from 4 to 47 days, and average time was 16 days (Fig. 1).

Characteristics Of Covid-19 Patients Receiving Cpt Therapy

A total of 163 COVID-19 patients received CPT therapy in Wuhan Huoshenshan Hospital, in which 124 (Male: 68, Female: 56) COVID-19 patients had no comorbidity of diabetes, including 5 of died cases, the mortality rate was 4.04%. The age of 124 COVID-19 patients ranged from 21 to 93 years old, average age was 63 years old. The type of comorbidities was range between 0 to 11, average number of comorbidities was 1 type. In addition, a total of 15 patients were treated in ICU (intensive care unit) and noticed of critical illness. The 124 COVID-19 patients receiving CPT therapy were divided into three classification, including 13 (10.48%) of mild patients, 90 (72.58%) of severe patients, and 21 (16.94%) of critical patients. The time of hospitalization ranged from 5 to 57 days, and average time was 27 days. In addition, the time of discharge from hospital of COVID-19 patients after receiving CPT ranged from 1 to 35 days, and average time was 11 days (Fig. 2).

Correspondingly, a total of 39 (Male: 23, Female: 16) out 163 COVID-19 patients receiving CPT therapy had comorbidity of diabetes, including 3 of died cases, the mortality rate was 7.69%. The age of 39 diabetes patients ranged between 21 to 93 years old, average age was 63 years old. A total of 8 diabetes

patients were treated in ICU (intensive care unit) and noticed of critical illness. Similarly, the 39 diabetes patients were divided into three classification, including 2 (5.13%) of normal patients, 27 (69.23%) of severe patients, and 10 (25.64%) of critical patients. The time of hospitalization ranged from 7 to 62 days, and average time was 26 days. While the time of discharge from hospital after receiving CPT ranged from 2 to 37 days, and average time was 13 days (Fig. 2).

Compared the baseline information of COVID-19 patients with diabetes comorbidity

The baseline information of 39 diabetes patients infected with COVID-19 receiving the CPT therapy was compared with that of 328 diabetes patients receiving traditional treatment. It was found that 8.2% mild COVID-19 patients receiving traditional treatment was below 50 years old, 29.6%, 40%, and 20% of patients with ages ranged between 50–60, 60–70, and 70–80 years old respectively. 2.2% of mild COVID-19 patients were over 80 years old. However, both ages between 50–60 and 60–70 years old of mild COVID-19 diabetes patients receiving CPT therapy accounted for 50%. Out of severe COVID-19 patients with traditional treatment, 51.9% of patients were over 60 years old, corresponding the patients receiving CPT therapy accounted for 81.5%. In addition, compared with 50% of critical COVID-19 patients receiving traditional treatment were over 70 years old, this percentage was 70% of critical patients receiving CPT therapy (Fig. 3A).

In 328 cases of COVID-19 diabetes patients receiving traditional treatment, 54.6% of patients were male, and 46.1% were female (Fig. 3B), including 42.1% of mild patients, 51.1% of severe patients, and 6.8% of critical patients respectively (Fig. 3C). Correspondingly, in 39 COVID-19 patients with comorbidity of diabetes receiving CPT therapy, 59% of male patients and 61% of female patients (Fig. 3B), including 5.1% of mild patients, 69.2% of severe patients, and 25.6% of critical patients respectively (Fig. 3C). Compared to 328 COVID-19 patients receiving traditional treatment with average 2 types of comorbidities, 39 diabetes patients receiving CPT therapy had average 3 types of comorbidities (Fig. 3D).

Analysis Of Blood And Biochemical Indicator Of Diabetes Patients

To examine the clinical outcome of CPT therapy for COVID-19 patients with comorbidity of diabetes, the blood and biochemical routine examination (Table 1, 2) reflecting kidney, liver and heart function of 39 COVID-19 patients receiving CPT therapy were compared to that of 328 diabetes patients receiving traditional treatment. The results indicated that in biochemical routine examination reflecting kidney function, the values of Urea and CysC of CPT therapy group were obviously higher than that of control group ($p < 0.05$) (Fig. 4A). In blood routine examination reflecting kidney function, although the values of LY%, MO% and EO% were within reference range, there were no obvious difference between CPT and non-CPT therapy group (Fig. 4B).

Table 1
Information of biochemical routine examination in this study

Test	Abbreviation	Reference range	Units
Alanine aminotransferase	ALT	9–60	U/L
Aspartate aminotransferase	AST	10–40	U/L
Total protein	TP	60–80	g/L
Albumin	ALB	35–50	g/L
Globulin	GLB	20–30	g/L
Total bilirubin	TBIL	1.7–20.4	μmol/L
Direct bilirubin	DBIL	0-6.8	μmol/L
Indirect bilirubin	IBIL	1.7–10.2	μmol/L
Total bile acid	TBA	0.1–10	μmol/L
Blood glucose	GLU	3.9–6.1	mmol/L
Urea nitrogen	Urea	7–20	mg/dL
Creatinine	Cre	44–106	μmol/L
Uric acid	UA	150–430	μmol/L
Alkaline phosphatase	ALP	40–160	U/L
γ-glutamyl transpeptidase	GGT	0–51	U/L
Cystatin C	CysC	0.51–1.09	mg/L
Creatine kinase	CK	24–170	U/L
Lactate dehydrogenase	LDH	100–300	U/L
alpha-hydroxybutyrate dehydrogenase	HBDH	90–182	U/L
Creatine kinase isoenzyme	CK-MB	0–16	U/L

Table 2
Information of blood routine examination in this study

Test	Abbreviation	Reference range	Units
White blood cell	WBC	4–10	10^9/L
Red blood cell	RBC	3.5–5.5	10^12/L
Hemoglobin	HB	110–160	g/L
Packed cell volume	PCV	0.37–0.54	vol%
Mean corpuscular	MCV	80–97	fL
Mean corpuscular hemoglobin	MCH	26.5–33.5	pg
Mean corpuscular hemoglobin concentration	MCHC	300–360	g/L
Red blood cell volume distribution width	RDWB	10–16	%
Blood platelet	PLT	100–300	10^9/L
Procalcitonin	PCT	< 0.5	ng/mL
Lymphocyte percentage	LY	17–48	%
Monocyte percentage	MO	4–10	%
Eosinophil percentage	EO	0.5-5	%
C-reactive protein	CRP	< 8	mg/L
Hypersensitive C-reactive protein	hs-CRP	0.06-10	mg/L

Correspondingly, in biochemical routine examination reflecting liver function, except the GLB values of patients receiving CPT therapy were obviously lower than that of non-CPT therapy patients (Fig. 4C), all other biochemical test results had not significant difference between CPT and non-CPT therapy patients. However, in blood routine examination reflecting liver function, the RBC values of diabetes patients receiving CPT therapy were significantly lower than that of diabetes patients receiving traditional treatment ($p < 0.01$), and the HB, PCV, and MCHV values of CPT therapy patients were obviously lower than traditional treatment patients ($p < 0.05$) (Fig. 4D). In addition, the RDWB values of CPT therapy patients were significantly higher than that of patients receiving traditional treatment ($p < 0.001$) (Fig. 4D).

Similarly, in biochemical and blood routine examination reflecting heart function, CK values of patients receiving CPT therapy were significantly lower than that of patients receiving traditional treatment ($p < 0.01$), and LDH values of CPT group were obviously higher than non-CPT group ($p < 0.05$) (Fig. 4E). It was worthy to note that the HBDH values of patients receiving CPT therapy were higher than that of patients receiving traditional treatment ($p < 0.05$), and these values were beyond the reference range (Table 2). Additionally, the Glu values of diabetes patients (average value was 8.0) after CPT therapy were similar with that of patients receiving traditional treatment (average value was 7.9) (Fig. 4F).

Cpt Therapy Was Effective For Covid-19 Patients With Diabetes

To evaluate the effectiveness of CPT therapy for COVID-19 patients with comorbidity of diabetes, the clinical outcome based on six categories of 39 patients receiving CPT therapy were compared to that of 328 patients receiving traditional treatment. Taking into consideration one point reduction as a criterion of clinical symptoms improving, the duration times of diabetes patients receiving traditional treatment varied from 1 day to 45 days, and the average duration time was 17 days (Fig. 5A). A total of 24.4% (80/328) of diabetes patients out of 328 COVID-19 cases matched this criterion, while 75.6% (248/328) of diabetes patients did not meet this criterion without clinical symptoms improving (Fig. 5B). Compared to these, the duration times of diabetes patients receiving CPT therapy varied from 1 day to 28 days, and the average duration time was only 10 days (Fig. 5A). It was worthy to note that high up to 69.2% (27/39) of COVID-19 patients matched this criterion with significantly clinical symptoms improving after CPT therapy (Fig. 5B).

Correspondingly, taking into consideration two points reduction as a criterion of clinical symptoms improving, in 328 COVID-19 patients with comorbidity of diabetes receiving traditional treatment, the duration times varied from 2 days to 39 days, and the average duration time was 27 days (Fig. 5C). Only 2.7% (9/328) of COVID-19 patients matched this criterion with clinical symptoms improving after traditional treatment such as anti-virus, steroids, and oxygen therapy (Fig. 5D). However, the duration times of diabetes patients receiving CPT therapy varied from 1 day to 28 days, and the average duration time was only 14 days (Fig. 5A). A total of 28.2% (11/39) of diabetes patients matched this criterion with clinical symptoms improving after CPT therapy (Fig. 5B). In conclusion, according to the six categories, the CPT therapy significantly improved the clinical outcome and reduced the duration time of COVID-19 patients with comorbidity of diabetes.

Discussion

As of early 2020, humanity all over the world was confronting the COVID-19 infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [17, 18]. A retrospective review of 72,314 COVID-19 infected cases by the Chinese Center for Disease Control and Prevention (China CDC), reported that 5% of COVID-19 patients were critical illness characterized by respiratory failure, septic shock, and/or multiple organ dysfunction or failure [19, 20]. The increased morbidity and mortality of COVID-19 patients was particularly seen in older and those presenting comorbidities conditions, commonly cardiovascular diseases and diabetes [21]. Emerging data suggested that individual with diabetes comorbidity were at high risk for COVID-19 infection, and increased risk for complications including death [22, 23]. To date, there have been only limited experimental studies directly addressing the role of hyperglycemia in the pathogenesis and prognosis of viral respiratory diseases [24]. Data of COVID-19 patients with diabetes is limited at present. Diabetes patients were present in 12.0% (367/3059) of COVID-19 infection in Wuhan

Huoshenshan Hospital of China, in which 21.7% of 69 fatalities due to COVID-19 with diabetes comorbidity.

At present, there are no effective vaccines, monoclonal antibodies (mAbs), or drugs available for treatment of COVID-19, although most are in rapid development and some may be available in a short time [25, 26]. Hence, human convalescent plasma is an option for COVID-19 treatment, and the convalescent plasma transfusion (CPT) therapy has been the subject of increasing attention, especially in the wake of large-scale epidemics [27]. In the early twentieth century, CPT therapy was used to stem outbreaks of viral diseases such as poliomyelitis, measles, mumps, and influenza [28]. A retrospective meta-analysis of eight investigations on the use of convalescent sera, involving 1703 patients during the H5N1 influenza virus pandemic suggested that those who received serum had lower mortality [29]. It has recently been suggested by US Food and Drug Administration (FDA) that administration and study of investigational CPT may provide a clinical effect for treatment of COVID-19 during the public health emergency. We had also conducted a system study to evaluate available data of Wuhan Huoshenshan Hospital of China for the clinical effectiveness of convalescent plasma for COVID-19 infection [30]. And in this study, an investigation of CPT therapy for COVID-19 patients with diabetes comorbidity was conducted. This will not only help to provide clinicians and scientists with an overview of scientific evidence on a potential treatment option of CPT, but also confirmed the effectiveness of CPT therapy for critically ill COVID-19 patients with diabetes.

According to the experience of SARS and severe influenza, convalescent plasma is recommended to use as early as possible because the production of endogenous IgM and IgG antibodies peaks at two weeks and four weeks after infection, respectively [31]. However, most patients admitted to Wuhan Huoshenshan Hospital have already been treated elsewhere and the duration from the onset of disease to admission usually exceeds four weeks. Optimal treatment for patient at relatively late course of COVID-19 was rather limited. A total of 163 COVID-19 patients admitted in Wuhan Huoshenshan Hospital receiving CPT therapy, in which 39 patients with comorbidity of diabetes. Fortunately, except for three critical male patients eventually died, CPT therapy was functional in 36 diabetes patients with COVID-19 infection, the cure rate was 92.3% (36/39). Although 94.9% (37/39) of diabetes illness were severe or critical COVID-19 patients, with average age was 68 years old, according to the six categories with one point reduction, the duration time of diabetes patients was only 10 days after receiving CPT therapy, while the duration time of patients receiving traditional treatment was 17 days. In addition, taking into consideration two points reduction as a criterion of clinical symptoms improving, only 2.7% of diabetes patients receiving traditional treatment meet this criterion, and the duration time was 27 days. While 28.2% of diabetes patients meet this criterion, and the duration time was 13 days after receiving CPT therapy. The results indicated the effectiveness of CPT therapy for diabetes patients with COVID-19 infection, especially severe and critical illness. To the best of our knowledge, this is a timely study evaluating the efficiency of CPT therapy in diabetes patients of COVID-19 infection with distinct laboratory and clinical features.

Conclusion

In conclusion, our study provided a comprehensive overview of COVID-19 patients with comorbidity of diabetes receiving convalescent plasma transfusion (CPT) therapy compared to patients receiving traditional treatment in Wuhan Huoshenshan Hospital. Based on baseline characteristics and clinical outcome of COVID-19 patients with diabetes comorbidity, it was demonstrated that CPT therapy was effective and beneficial for COVID-19 patients, including severe or critical illness, without obvious adverse effects observing during the treatments. The CPT therapy also significantly improved the clinical outcome of COVID-19 infection with diabetes, especially the duration based on six categories compared to the patients with traditional therapy.

Declarations

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethical Committee of Wuhan Huoshenshan Hospital, Wuhan, China. The patients provided their written informed consent to participate in this study.

Consent for publication

The written informed consent was obtained from each patient.

Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflicts of interest with this work.

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Author’s contributions

WD conducted data analysis and wrote the manuscript; JW and TL analyzed the data and generated the figures; JS, RP, BH, TL, YG, and YY conducted data analysis; JZ, MZ, NL, YH, QW, and WL contributed comments during the writing; XX conceived the study.

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Figures

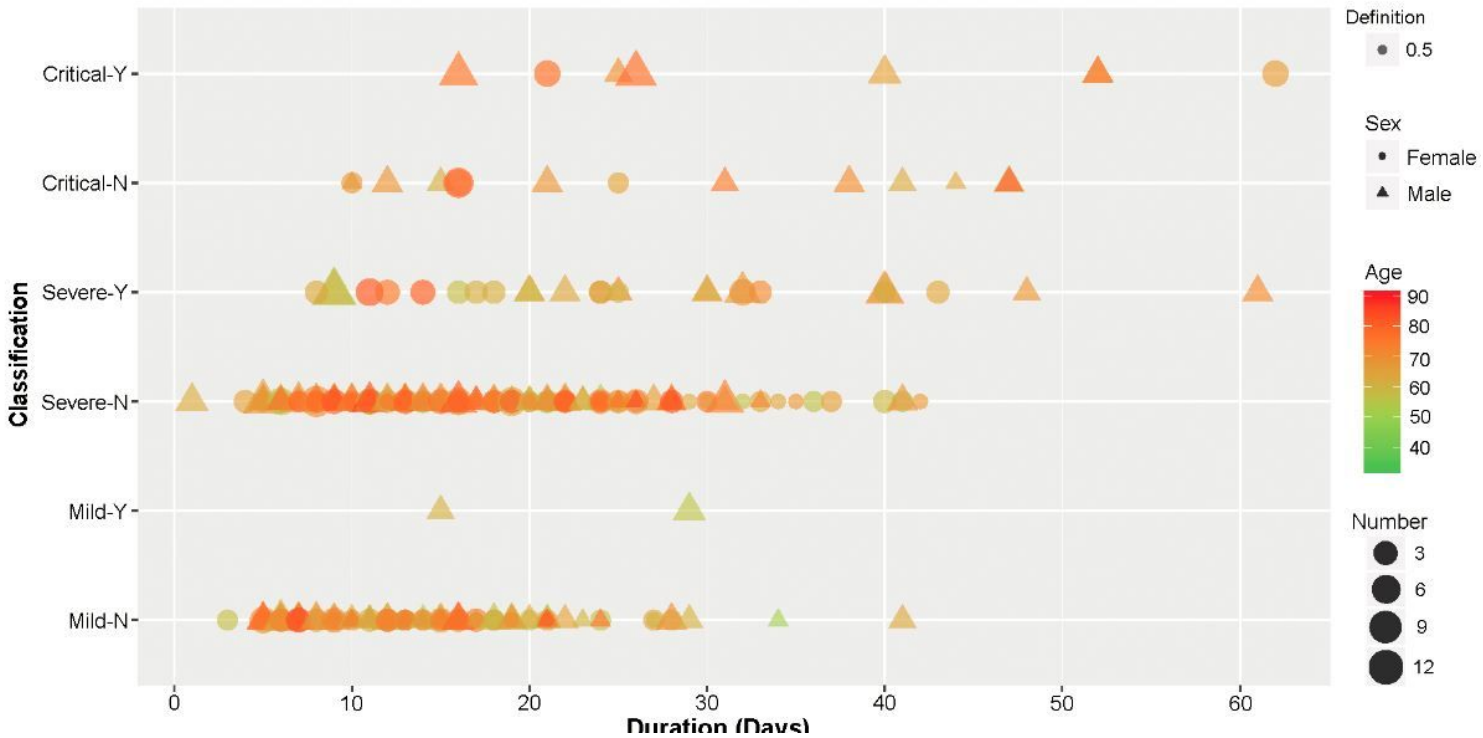

Figure 1

Heat map of characteristics of COVID-19 patients receiving traditional treatments. A total of 2896 COVID-19 patients receiving traditional treatments admitted in Wuhan Huoshenshan Hospital from February 4 to April 12, 2020, in which 328 patients with comorbidity of diabetes. The severity degree of each patient was determined according to the clinical classification criterion of Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission (7th trail version). N, COVID-19 patients without comorbidity of diabetes; Y, COVID-19 patients with comorbidity of diabetes; Number, the number of comorbidities. The map excluded 37 patients without classification, and 61 died cases.

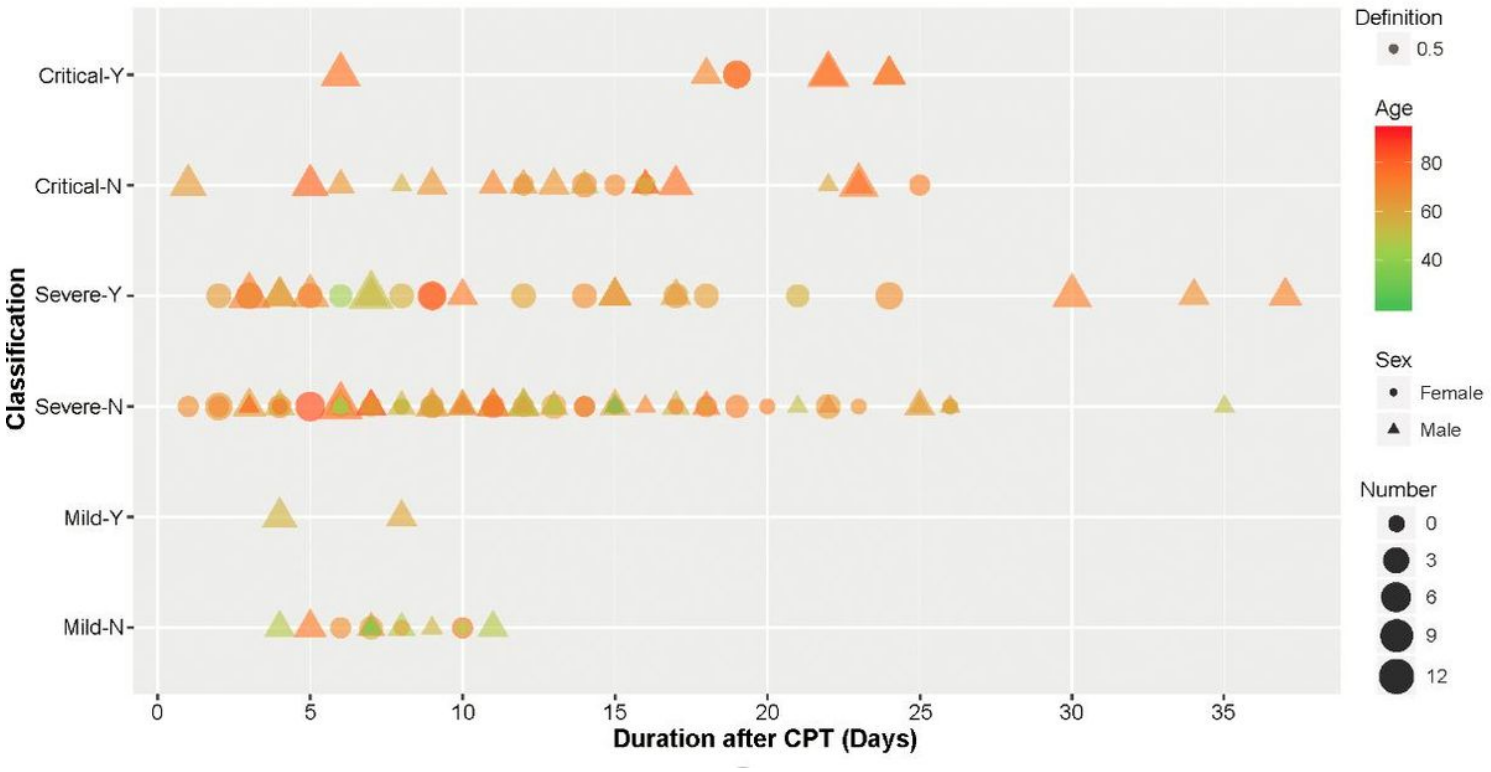

Figure 2

Heat map of characteristics of COVID-19 patients receiving CPT therapy. A total of 163 COVID-19 patients receiving CPT therapy admitted in Wuhan Huoshenshan Hospital from February 4 to April 12, 2020, in which 39 patients with comorbidity of diabetes. The severity degree of each patient was determined according to the clinical classification criterion of Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission (7th trail version). N, COVID-19 patients without comorbidity of diabetes; Y, COVID-19 patients with comorbidity of diabetes; Number, the number of comorbidities. The map excluded 8 died patients.

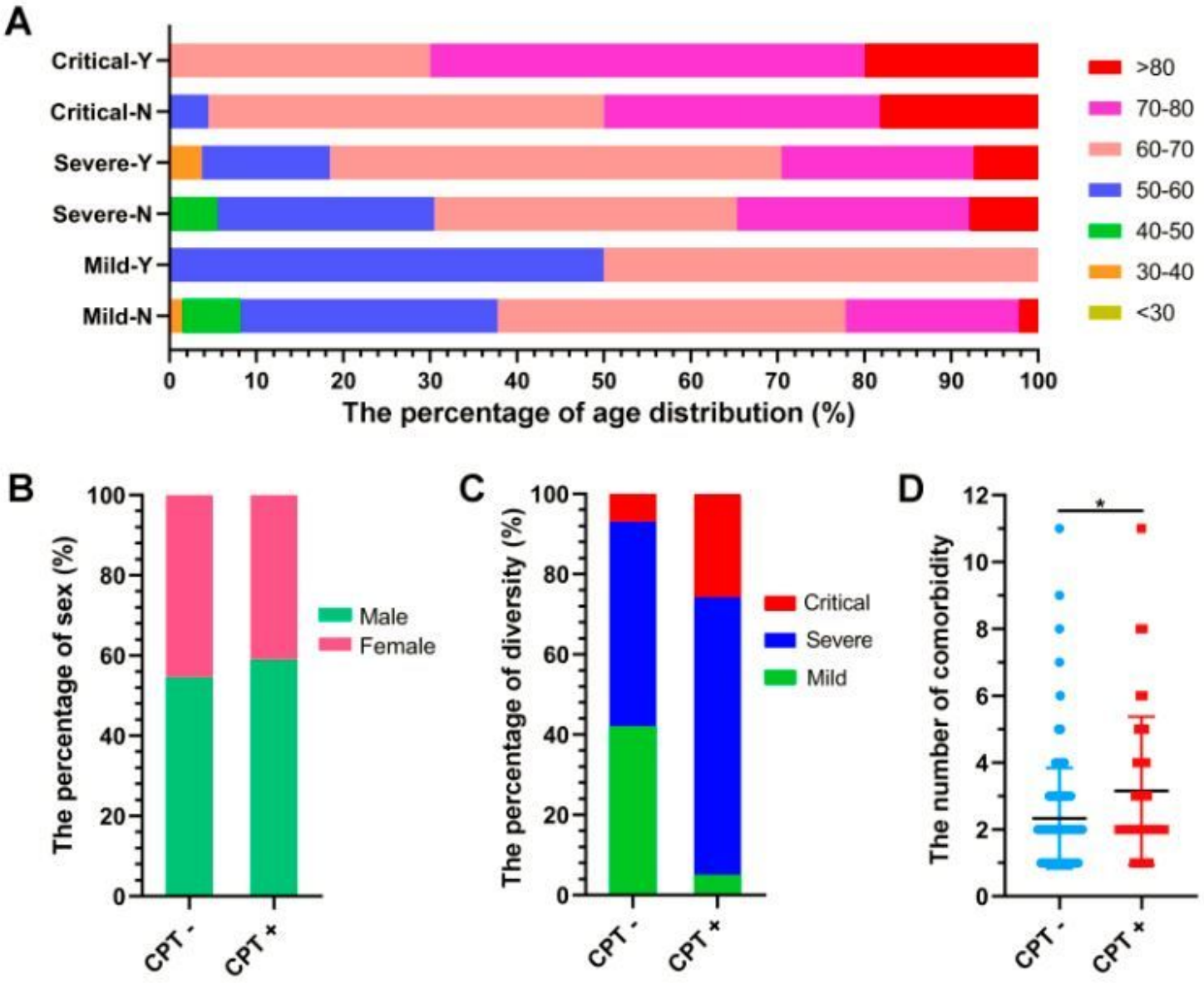

Figure 3

Baseline characteristics of COVID-19 patients with diabetes comorbidity. (A) The percentage of age distribution in mild, severe and critical COVID-19 patients. N, 328 COVID-19 patients with diabetes comorbidity receiving traditional treatment. Y, 39 COVID-19 patients with diabetes comorbidity receiving CPT therapy. (B) The percentage of sex distribution of COVID-19 patients with diabetes comorbidity. (C) The percentage of clinical classification distribution of COVID-19 patients with diabetes comorbidity. (D) The number of comorbidities of COVID-19 patients with diabetes comorbidity. CPT -, 328 COVID-19 patients with diabetes comorbidity receiving traditional treatment. CPT +, 39 COVID-19 patients with diabetes comorbidity receiving CPT therapy. *, $p < 0.05$.

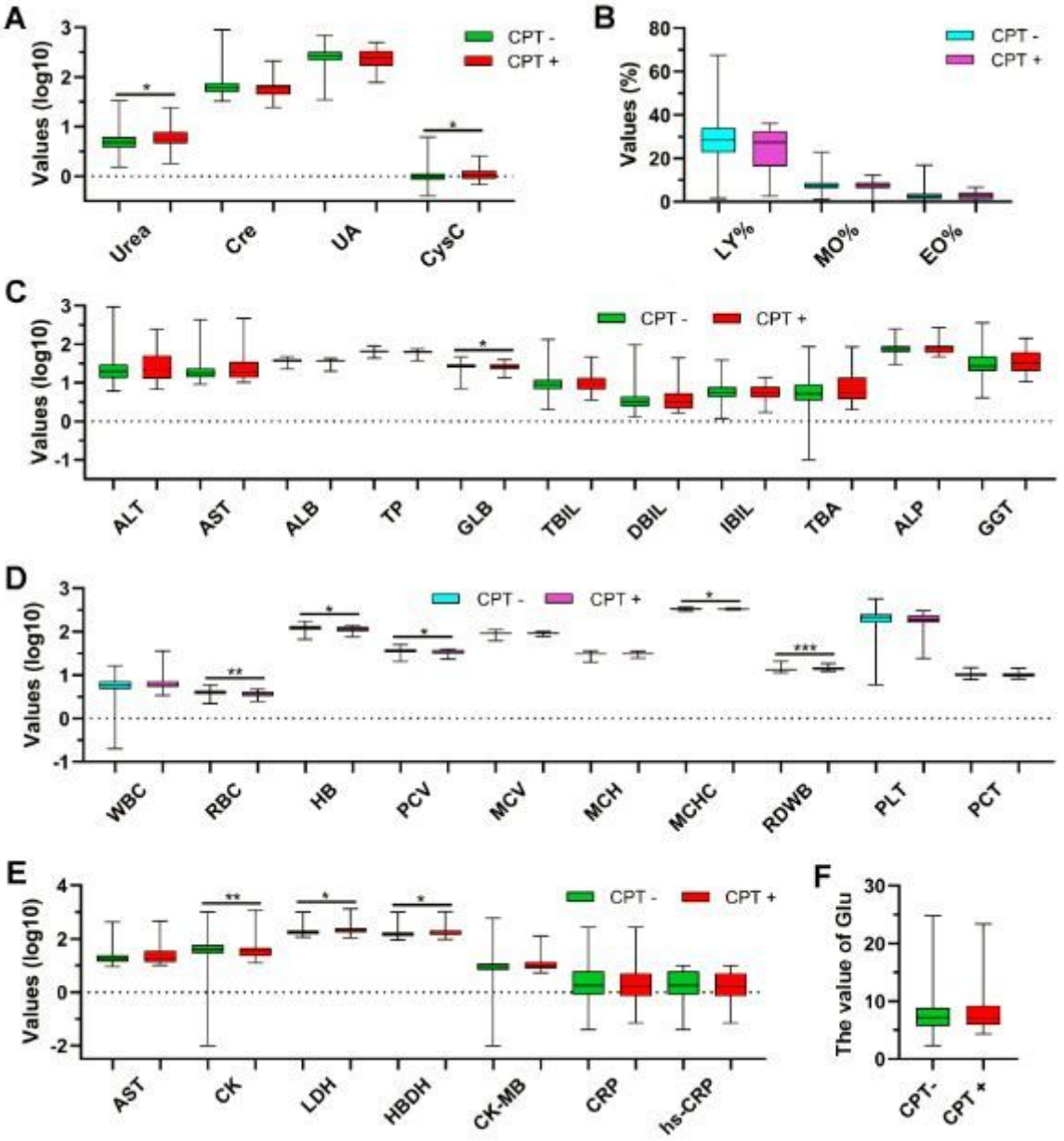

Figure 4

The blood and biochemical routine examination of COVID-19 patients with diabetes comorbidity. (A) The biochemical routine examination of COVID-19 patients reflecting kidney function. (B) The blood routine examination of COVID-19 patients reflecting kidney function. (C) The biochemical routine examination of COVID-19 patients reflecting liver function. (D) The blood routine examination of COVID-19 patients reflecting liver function. (E) The blood and biochemical routine examination of COVID-19 patients reflecting heart function. (F) The Glu values of COVID-19 patients with diabetes comorbidity. CPT -, 328 COVID-19 patients with diabetes comorbidity receiving traditional treatment. CPT +, 39 COVID-19 patients with diabetes comorbidity receiving CPT therapy. *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$.

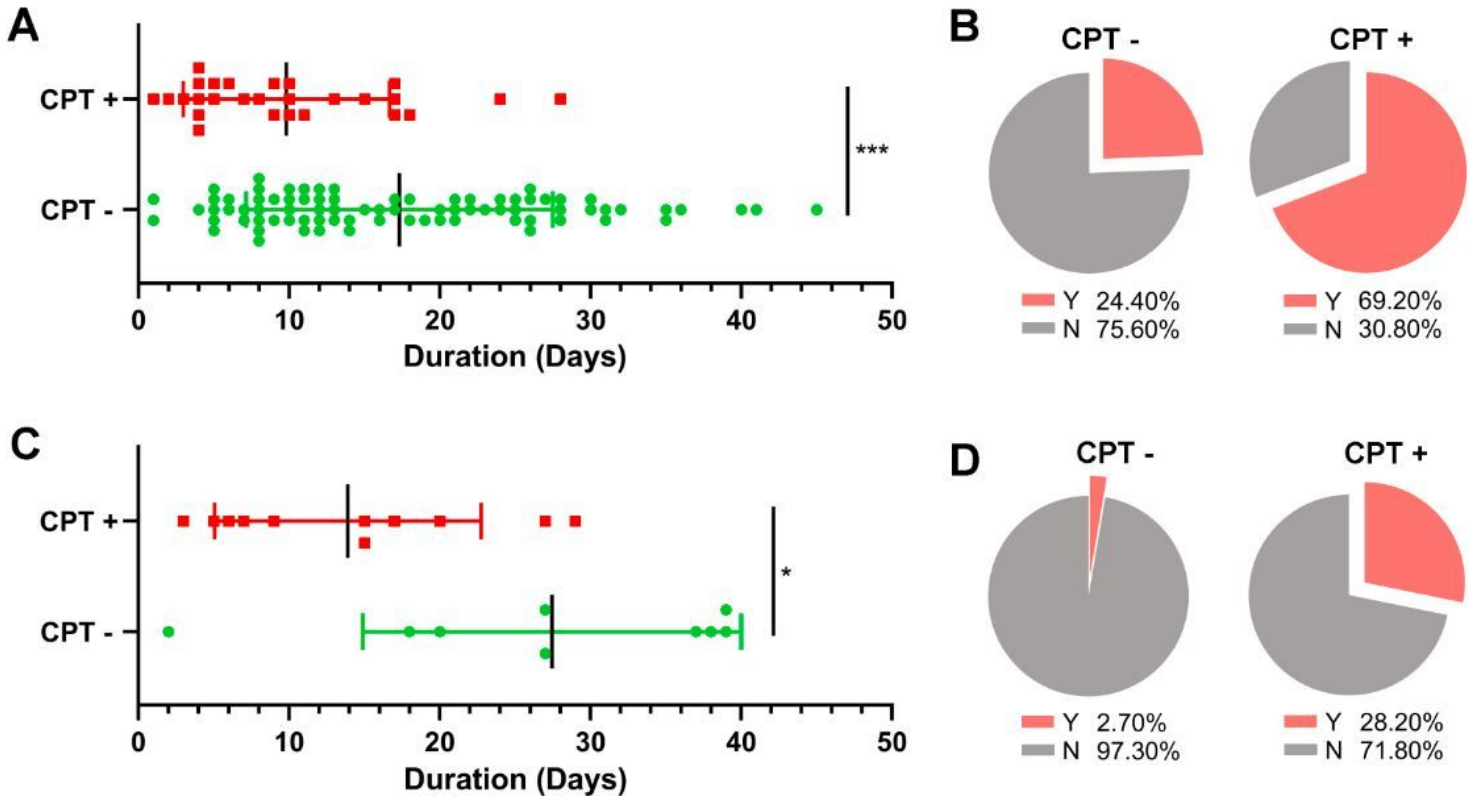

Figure 5

The clinical outcome based on six categories of COVID-19 patients with diabetes comorbidity. (A) The time of duration of COVID-19 patients with one point reduction. (B) The percentage of COVID-19 patients with one point reduction. (C) The time of duration of COVID-19 patients with two points reduction. (D) The percentage of COVID-19 patients with two points reduction. N, COVID-19 diabetes patients without one or two points reduction. Y, COVID-19 diabetes patients with one or two points reduction. CPT -, 328 COVID-19 patients with diabetes comorbidity receiving traditional treatment. CPT +, 39 COVID-19 patients with diabetes comorbidity receiving CPT therapy. *, $p < 0.05$, ***, $p < 0.001$.