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Original Article

Metabolic alkalosis in type 2 diabetic patients with severe COVID-19

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Abstract: Background: Coronavirus disease 2019 (COVID-19) is a newly notifiable pneumonia disease spreading rapidly and causes disability and deaths worldwide. Type 2 diabetes (T2D), one of the most common metabolic disorder, is suggested as one of the risk factors of COVID-19 and contributes to its severity and mortality. Therefore, we investigated the characteristics of the patients suffered from severe COVID-19 in order to provide proper treatments. Methods: This study retrospectively reviewed data of 24 patients with severe COVID-19. Eleven patients with T2D and 13 with normal glucose tolerance (NGT) were compared by various indicators and followed by statistical analysis. Results: In the T2D group, arterial blood pH, serum bicarbonate (SB), actual bicarbonate (AB), whole blood alkaline excess (BE), and base excess in the extracellular fluid Compartment (BEecf) significantly exceeded the upper limit of stock. The pH and SB in the T2D group were considerably higher than those of the NGT group ($P<0.05$). After treated for more than two days with both the herbal prescription of traditional Chinese medicine and beraprost sodium, breathing difficulties as well as metabolic alkalosis were significantly improved. Conclusions: Severe lung damages in T2D patients with severe COVID-19 might behave as a mixed acid-alkaline imbalance disorder due to metabolic alkalosis. Breathing difficulties and metabolic alkalosis could be improved after the treated with traditional Chinese medicine and beraprost sodium. Although a small number of patients were included in this study, our findings provide an efficient indicator for treating T2D diabetic patients with severe COVID-19.

Keywords: Coronavirus disease 2019 (COVID-19), pneumonia, type 2 diabetes (T2D), metabolic alkalosis

Introduction

A severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2), subsequently called coronavirus disease 19 (COVID-19), has ravaged the world and was declared a pandemic by the World Health Organization (WHO) in March 2020 [1, 2]. SARS-CoV-2 is a beta coronavirus with sequence homology with SARS-CoV (79%) and distant similarities (50%) with Middle East respiratory syndrome coronavirus (MERS-CoV) [3]. It is highly contagious and transmitted between individuals through aerosolized droplets and contact with infected surfaces [4]. In general, severe cases develop rapidly into pneumonia after infection with exacerbated respiratory symptoms. Such pneumonia quickly became a newly recognized disease and spread rapidly throughout the world affecting more than 100 countries [5].

The factors affecting the severity and mortality of COVID-19 could be age, delayed referral to a hospital, hypertension, diabetes and obesity [5-11]. Patients with type 2 diabetes (T2D) seem to have an increased risk for more severe COVID-19 infections, especially those with poorly controlled blood glucose level [12, 13]. COVID-19 patients with comorbidity of diabetes are around 12.1-33.8% [15-17]. Studies showed that the prevalence of diabetes in patients with mild COVID-19 ranged 5.7-5.9%, and that in patients with severe COVID-19 raised to 22.2-26.9% [10, 17]. A higher mortality rate was also showed in diabetic patients with COVID-19 [12].

Studies revealed that COVID-19 patients with diabetes have a high risk of requiring ICU admission [20]. According to the Chinese Centers for Disease Control and Prevention, COVID-19 case-fatality rates in patients with diabetes were around 7.3% versus 2.3% in the general Chinese population. Individuals with diabetes are particularly vulnerable to respiratory viral infections, such as influenza A infection, severe acute respiratory syndrome and Middle East respiratory syndrome [18, 19]. A study including 138 hospitalized Covid-19 patients showed that 22.2% (8/36) patients treated in the ICU coexisting with diabetes and 5.9% (6/102) in non-ICU [17]. All the results indicate that diabetes is a key risk factor for patients with severe COVID-19 and indicate the need for supervision of these patients [21]. In fact, the appropriate management of COVID-19 in people with diabetes has been debated actively during the pandemic, especially with regards to drugs best suited for glycemic control that may also reduce the risk of infection and attenuate the severity of complications [9].

In T2D patients with severe COVID-19, the fluctuation ranges can be predicted from the equilibrium between HCO_3 and PCO_2 when an acid-base imbalance occurs due to simple chronic respiratory acidosis, chronic respiratory alkalosis, metabolic acidosis, or metabolic alkalosis. Although metabolic acidosis is a common acid-base balance disorder in severe COVID-19, a severe lack of oxygen and insufficient tissue perfusion can also lead to metabolic alkalosis, which is the most common cause of death [6, 7, 14, 22]. Metabolic alkalosis is often associated with hypokalemia/hypopotassemia and hyponatremia disorder, making patients prone to life-threatening ventricular arrhythmias associated with potassium loss [22-26]. The most common causes of metabolic alkalosis are insufficient body capacity, potassium consumption, chlorine consumption and loss of anions due to diuretics [27, 28]. Low levels of potassium at admission have been associated with poor prognosis and severe disease but little is known about the dynamics.

So far, there is no specific drug to treat COVID-19 infection in the clinic. Due to the COVID-19 infection-mediated systemic inflammatory responses and system dysfunction, different degrees of damages may occur in the human body. Analysis of the characteristics based on the existing COVID-19 symptoms provide more information for effective treatment. In this study, the clinical characteristics and laboratory data of 24 COVID-19 patients with or without T2D were analyzed. We found that high incidence of severe lung damages in severe COVID-19 patients with T2D may behave as a mixed acid-alkaline imbalance disorder due to metabolic alkalosis. This suggests the importance of blood gas and electrolyte analysis in clinic for treatment consideration.

Methods

Study design

This retrospective, observational, single center study collected data from the records of patients with severe COVID-19 admitted to Central Hospital of Wuhan, China, and hospitalized in the general ward from January to March, 2020.

Patients/subjects

A total of 24 patients met the diagnostic criteria of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (version 7) released by the National Health Commission & State Administration of Traditional Chinese Medicine, including 11 cases with confirmed T2D and 13 cases with normal glucose tolerance (NGT) (**Table 1**). Inclusion criteria were: (1) respiratory distress with RR ≥ 30 breaths/min; (2) oxygen saturation ≤ 93% under resting state; (3) CT image shows multiple lesions in both lungs; (4) pharyngeal swab sampling positive for nucleic acid of SARS-CoV-2; (5) influenza A and B virus, adenovirus, syncytial virus, and mycoplasma chlamydia are all negative. In addition, patients with diabetic ketoacidosis were excluded in this study.

Laboratory test

Comprehensive blood tests were performed on all the patients during their hospitalization. Arterial blood gas tests included pH, PO_2, PCO_2, standard bicarbonate (SB), actual bicarbonate (AB), BE (base excess), BEecf (base excess in extracellular fluid), oxygen saturation values and lactate. Other tests included fasting blood glucose (FBG), alanine transaminase (ALT), aspartate transaminase (AST), total protein, albumin, creatinine, triacylglycerol (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), C-reactive protein (CRP), fibrinogen, D-dimer, erythrocyte

Table 1. Characteristics and laboratory examination results of the included severe COVID-19 patients

Term	NGT	DM	*p*-value
Baseline characteristic			
Case (no.)	13	11	
Age	57.08±8.85	66.36±11.43	0.041
Gender			0.206
Male	3 (23.08%)	6 (54.55%)	
Female	10 (76.92%)	5 (45.45%)	
Medical history			
Hypertension	4 (30.77%)	9 (81.82%)	0.012
Heart disease	1 (7.69%)	3 (27.27%)	0.200
Gastrointestinal diseases	4 (30.77%)	3 (27.27%)	0.999
Complications			
Fever	7 (53.85%)	8 (72.73%)	0.341
Chilly	2 (15.38%)	4 (36.36%)	0.237
Cough	7 (53.85%)	9 (81.82%)	0.148
Productive cough	3 (23.08%)	3 (27.27%)	0.813
Chest tightness	4 (30.77%)	3 (27.27%)	0.999
Palpitations	2 (15.38%)	2 (18.18%)	0.034
Shortness of breath	3 (23.08%)	2 (18.18%)	0.087
Lack of energy	5 (38.46%)	4 (36.36%)	0.011
Muscle Aches	3 (23.08%)	4 (36.36%)	0.659
Headache	2 (15.38%)	1 (9.09%)	0.216
Loss of appetite	3 (23.08%)	3 (27.27%)	0.813
Diarrhea	1 (7.69%)	1 (9.09%)	0.015
Laboratory examination			
PCT (ng/ml)	0.05±0.015	0.07±0.039	1.102
FBG (mmol/L)	5.45±1.00	9.14±3.13	0.001
ALT (U/L)	38.13±75.44	53.74±77.52	0.623
AST (U/L)	23.61±20.42	27.45±16.90	0.625
TP (g/L)	66.14±7.17	58.53±12.09	0.069
ALB (mmol/L)	39.04±4.43	34.75±3.41	0.016
Cr (umol/L)	59.26±22.44	71.43±21.13	0.188
TG (mmol/L)	1.38±0.52	1.42±0.52	0.883
TC (mmol/L)	4.11±1.23	4.13±1.77	0.967
HDL (mmol/L)	1.13±0.18	1.15±0.42	0.876
LDL (mmol/L)	2.66±1.22	2.28±1.35	0.475

Abbreviation: NGT, normal glucose tolerance; DM, diabetes mellitus; PCT, Procalcitonin; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, Total protein; ALB, Albumin; Cr, Creatinine; TG, Triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

sedimentation rate (ESR), procalcitonin and electrolytes (i.e. K^+, Na^+, Cl^-, Ca^{2+} and P^{3+}).

Treatment

We treated patients with two kinds of medicines combined to improve their microcirculation. One is the herbal prescription of traditional Chinese medicine, which is "Pneumonia Formula No. 1" for the national treatment of COVID-19. Another is beraprost sodium tablets. Beraprost sodium was known to maintain blood flow of tissues though several mechanisms, including dilating blood vessels, antiplatelet aggregation, vascular endothelial protection, growth inhibition of smooth muscle cells and anti-inflammatory effects [29]. This drug does not increase myocardial oxygen consumption and is the preferred drug for patients with chronic arterial disease with a high risk of cardiovascular disease. In 2013, beraprost sodium was recommended for the treatment of diabetic patients complicated with lower-extremity arterial lesions according to the "expert consensus of the diagnosis and treatment measures for the Chinese elderly patients with type 2 diabetes" and "joint recommendations for the screening and management for type 2 diabetes combined with lower-extremity arterial lesions" [30]. Meanwhile, patients were encouraged to eat high-protein foods and increase the amount of oral solution.

Ethical considerations

The project was conducted following the Helsinki Declaration, and the study protocol was reviewed and approved by the Internal Review Board of Central Hospital of Wuhan, China, before this study was conducted. Signed informed consent was waived because of the retrospective study design. The IRB number is 2021-001.

Statistical analysis

All data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as counts (percentages). Continuous

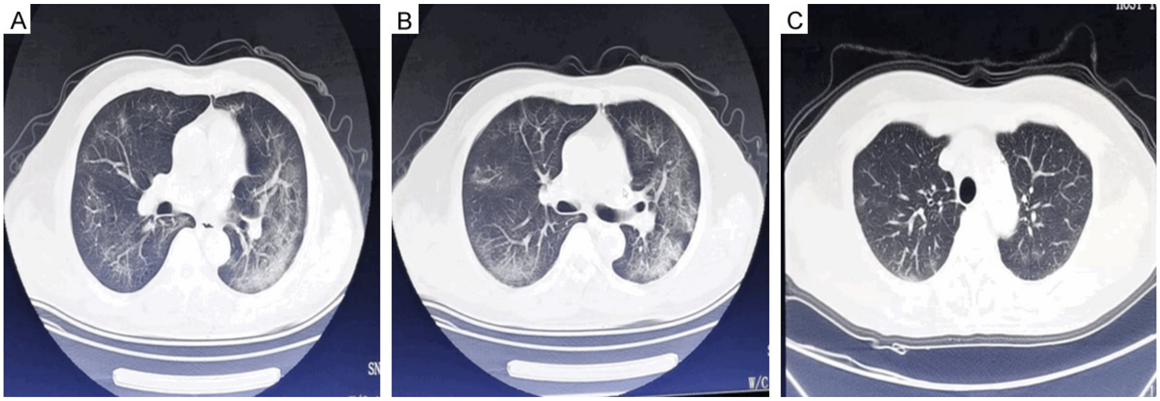

Figure 1. Chest CT scan from a 58-year-old COVID-19 male case without T2D, showing fever for nine days and breathing difficulty for five days. A. The first level. B. The second level. C. The third level.

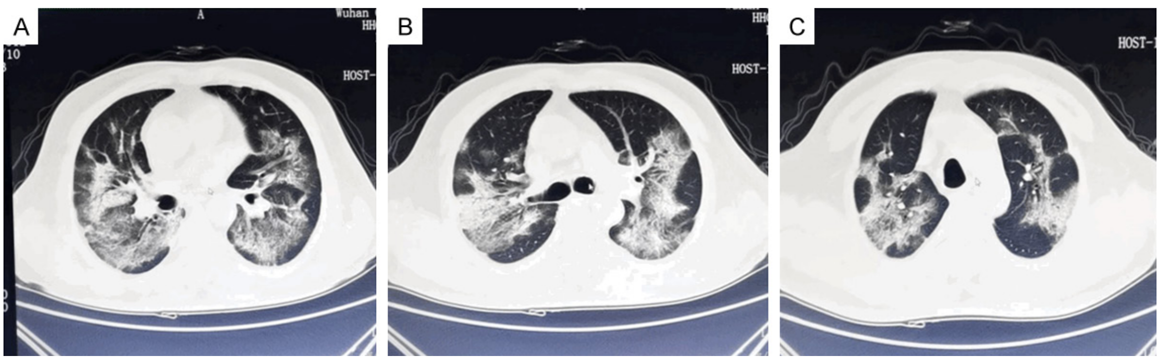

Figure 2. Chest CT scan from a 68-year-old COVID-19 male case complicated with T2D, showing fever and cough for ten days, and chest pain and shortness while breathing for five days. A. The first level. B. The second level. C. The third level.

variables were compared by independent t test, whereas categorical data were analyzed using Chi-square test. Pearson correlation was used in measure of the strength of the association between acid-base balance parameters and other blood tests. All tests were 2-tailed and a significance level of 0.05 was adopted.

Results

Study population

All patients with COVID-19 in this study were severe patients with pharynx swabs testing positive for SARS-CoV-2 nucleic acid, normal procalcitonin and multiple lesions of lung CT. All patients had extensive lung damage (**Figures 1** and **2**) with severe hypoxemia. The main signs of CT are unilateral or bilateral lung multifocal ground-glass opacities and consolidation shadows, showing a “crazy paving” pattern. Lesions were mainly distributed in the peripheral and subpleural areas of the lung, but also along Broncho vascular bundles with visible air Broncho line signs and reticular and/or interlobular septal thickening, accompanied by chest cavity fluid or lymph node swelling.

The comparisons of essential characteristics, medical history and complications between diabetes and NGT groups were shown in **Table 1**. There are 11 patients with T2D in the diabetes group, 6 cases of males and 5 cases of females. There are 13 patients without T2D in the NGT group, in which 3 cases of males, 10 cases of females. The mean age was 66.36±11.43 years and 57.08±8.85 years in the diabetes and NGT groups, respectively, with significant difference ($P<0.05$).

The medical history of the NGT group is hypertension (30.77%), heart disease (7.69%) and gastrointestinal diseases (30.77%); that of the diabetes group is hypertension (81.82%),

Table 2. Arterial blood gas and electrolyte analysis of the severe COVID-19 patients

Term	NGT	DM	*p*-value
Arterial blood gas analysis			
pH	7.41±0.05	7.45±0.04	0.047
PCO_2 (mmHg)	44.46±5.72	45.18±8.98	0.814
PO_2 (mmHg)	81.92±11.08	72.27±15.78	0.093
SB (mmol/L)	26.95±1.80	29.86±4.30	0.036
AB (mmol/L)	27.73±1.80	30.51±6.06	0.138
BE	2.91±2.43	5.73±5.31	0.100
BEecf	3.34±2.60	8.47±8.89	0.090
SO_2%	96.54±3.26	87.09±27.69	0.286
LA (mmol/L)	2.46±1.18	2.09±1.08	0.433
Urine pH	6.23±0.48	6.09±0.44	0.479
Urine SG	1.02±0.00	1.02±0.00	0.986
Electrolyte			
K^+ (mmol/L)	4.15±0.53	4.12±0.46	0.917
Na^+ (mmol/L)	141.12±2.97	141.86±2.96	0.544
Cl^- (mmol/L)	104.19±3.25	103.95±4.97	0.885
Ca^{2+} (mmol/L)	2.21±0.17	2.13±0.18	0.231
P^{3-} (mmol/L)	1.13±0.18	0.99±0.18	0.066

Abbreviation: NGT, normal glucose tolerance; DM, diabetes mellitus; SB, standard bicarbonate; AB, actual bicarbonate; BE, base excess; BEecf, base excess of extracellular fluid; LA, lactate; SG, Urine Specific Gravity.

heart disease (27.22%) and gastrointestinal diseases (27.22%). The rate of patients with hypertension history was significantly higher in the diabetes group than in the NGT group ($P< 0.05$), providing evidence that hypertension could be another risk factor of severe COVID-19 patients with diabetes.

The main symptoms for diabetes group are fever (72.73%), cough (81.82%), chest tightness (27.27%), shortness of breath (18.18%), loss of appetite (27.27%) and diarrhea (9.09%); those for NGT group are similar, including fever (53.85%), cough (53.85%), chest pain (30.77%), shortness of breath (23.08%), loss of appetite (23.08%) and diarrhea (7.69%). There were significant differences between NGT and diabetes group ($P<0.05$) in terms of palpitations, lack of breath, and diarrhea. In regard to laboratory examination, FBG in the diabetes group was significantly higher than in NGT groups, whereas ALB in diabetes group was significantly lower than in non-diabetic groups ($P<0.05$). No statistical differences were found in the levels of TG, TC, HDL and LDL between the two groups.

Arterial blood gas analysis and electrolyte examination

Arterial blood pH and SB in diabetes group were significantly higher than NGT group ($P<0.05$). Although diabetes group has a higher PCO_2, AB, BE and BEecf than NGT group, there were no significant differences between two groups (**Table 2**).

Correlation of PO_2, SB and LA

For these severe patients with COVID-19, PO_2 had a significant positive correlation with SO_2, ALB, Ca^{2+} and P^{3+}, but had a significant negative correlation with PCO_2, SB, AB, BE, BEecf and FBG ($P<0.05$). SB had a significant positive correlation with pH, PCO_2, AB, BE, BEecf and FBG, but had a negative correlation with PO_2, SO_2, Cl^-, P^{3+}, TP and ALB ($P<0.05$). LA had a significant negative correlation with pH, but there was no correlation with LA in other examination data (**Table 3**).

Treatment

After treatment of two days, patients had significantly improved breathing difficulties with a quick increase of PO_2 from 45 mmHg to 65 mmHg under an immediate adjustment that gradually reduced the oxygen absorption concentration. Metabolic alkalosis was also gradually improved at the same time. Four months after, CT images of COVID-19 patients with diabetes showed that lungs were scattered in high ropes, small patches of fuzzy shadow and cystic translucent areas (**Figure 3**). Pulmonary function prompted mild restrictive ventilation disorders. These patients had COVID-19 IgG antibody (+), virus IgG antibody (-), erythrocyte sedimentation rate 50 mm/h. The routine blood tests, biochemical examination and blood gas analysis results were all normal. Therefore, it is necessary to treat the severe hypoxemia for severe COVID-19 patients through timely adoption of high-flow oxygen absorption. On the other hand, timely evaluation of microcirculation disorder, chronic inflammation and blood hypercoagulation as early as possible is important for patients to improve hypoxia and acid-base balance disorders.

Table 3. Correlation between acid-base balance parameters and other blood tests

Term	PO_2 r (*p*-value)[a]	SB r (*p*-value)[a]	LA r (*p*-value)[a]
Arterial blood gas analysis			
pH	-0.087 (0.687)	0.533 (0.007)	-0.407 (0.049)
PCO_2	-0.496 (0.014)	0.574 (0.003)	0.189 (0.377)
PO_2	-	-0.534 (0.007)	-0.296 (0.161)
SB	-0.534 (0.007)	-	-0.217 (0.308)
AB	-0.450 (0.027)	0.900 (<0.0001)	-0.147 (0.494)
BE	-0.691 (<0.0001)	0.896 (<0.0001)	-0.034 (0.874)
BEecf	-0.497 (0.013)	0.923 (<0.0001)	-0.144 (0.501)
SO_2	0.629 (0.001)	-0.427 (0.038)	-0.148 (0.491)
LA	-0.296 (0.161)	-0.217 (0.308)	-
Electrolyte			
K^+	0.203 (0.342)	-0.080 (0.709)	-0.202 (0.344)
Na^+	-0.061 (0.778)	-0.017 (0.936)	-0.005 (0.982)
Cl^-	0.136 (0.527)	-0.469 (0.021)	0.029 (0.895)
Ca^{2+}	0.572 (0.004)	-0.307 (0.144)	0.036 (0.867)
P^{3+}	0.454 (0.026)	-0.614 (0.001)	0.040 (0.852)
Laboratory examination			
FBG	-0.567 (0.004)	0.526 (0.008)	0.014 (0.948)
ALT	-0.111 (0.604)	-0.218 (0.305)	0.094 (0.661)
AST	-0.020 (0.927)	-0.137 (0.524)	-0.019 (0.931)
TP	0.249 (0.241)	-0.467 (0.021)	0.082 (0.704)
ALB	0.618 (0.001)	-0.610 (0.002)	-0.114 (0.595)
Cr	-0.198 (0.353)	0.119 (0.579)	-0.140 (0.514)
TG	0.126 (0.556)	-0.209 (0.326)	0.111 (0.607)
TC	-0.026 (0.906)	-0.047 (0.827)	0.092 (0.668)

[a]Pearson correlation.

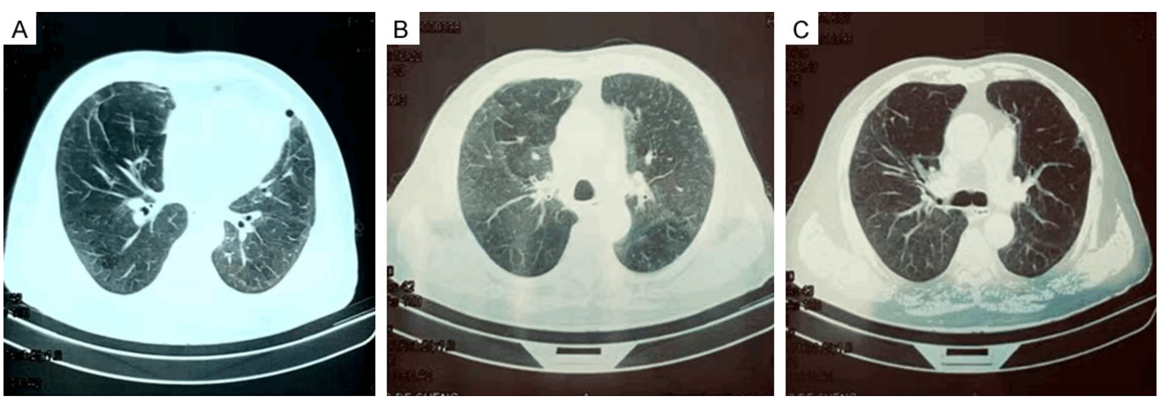

Figure 3. Chest CT scan from the same case as **Figure 2**, showing the reexamination after four months of illness. A. The first level. B. The second level. C. The third level.

Discussion

The COVID-19 pandemic is the defining global health crisis of our time, and it has become the most significant challenge we have recently encountered. Obvious breathing difficulties or hypoxemia can appear due to severe lung damage after a week of onset [31]. The progress or reversion of the disease condition varies among COVID-19 patients. In addition, diabetes was associated with mortality and severe COVID-19 symptoms in patients with COVID-19 [14]. Diabetic patients with uncontrolled blood sugar levels are more susceptible to develop severe symptoms, resulting in prolonged hospitalization and increased risk of death [32]. In addition, risks of developing critical illness caused by COVID-19 in patients with diabetes or obesity was raised proportionately to the presence of other pre-existing medical conditions, such as hypertension, cardiovascular disease, and chronic kidney disease.

Studies reported that clinical symptoms of COVID-19 infection are diverse and most patients with severe COVID-19 are elderly individuals [6-8, 14], along with a high prevalence of pre-existing diabetes of approximately 12% in Chinese adult patients [21]. The study results showed that arterial blood pH, SB, AB, BE and BEecf in diabetes group were significantly higher than the control, and that BE and BEecf in diabetes group were considerably higher than those in NGT group. PO_2 in diabetes group was negatively correlated with SB, AB, BE, and FBG, indicating the reduction of blood oxygen pressure is closely related to metabolic alkalosis. In this study, all patients were not treated with diuretics in the course of the disease, excluding the metabolic alkalosis caused by diuretics.

Most of the severe patients in this study were accompanied by fever, poor appetite, diarrhea and other symptoms in the course of the disease, and about 30% of the patients had gastrointestinal disorders. These patients had a reduction in food intake with an increase of their consumption in the course of the disease. At this point, the following symptoms can appear: (1) Insufficient dietary intake in K^+, Na^+ and Cl^-, and consumptive hypoproteinemia. (2) Reduced blood volume, metabolic disorders of surrounding tissues and accumulation of lactic acid. (3) Gastrointestinal diseases with an increased loss of stomach acid. These can transfer intracellular liquid HCO_3^- to extracellular liquid and decrease extracellular hydrogen ions in patients with severe COVID-19, leading to metabolic alkalosis. In turn, metabolic alkalosis can further aggravate the following physiological phenomena: (1) pulmonary hypoventilation, hypoxemia and hypercarbonemia; (2) reflex inhibition of hypoxic pulmonary vasoconstriction, unopened at the bottom of the lung base, and decreased V/Q ratio, further aggravating hypoxemia; (3) a left-shift of oxygen dissociation curve with decreased oxygen release and transport to tissues and increased acid metabolites. In this study, patients with T2D had lactic acid accumulation; ALB was significantly lower than in non-diabetic groups, and PO_2 was positively correlated with ALB. All these phenomena indicate that the metabolic alkalosis indeed occurred in these patients.

In this study, the plasma K^+, Na^+, and Cl^- of all patients were within normal range. It may be related to the patient's persistent fever, poor appetite and diarrhea, resulting in insufficient volume capacity. It further leads to reduced glomerular filtration rate, decreased renal sodium storage and secondary hypoaldosteronism. Aldosterone reduction can cause further deterioration of metabolic alkalosis by stimulating the increase of H^+-ATPase pump activity in the intercalated cells of kidney collecting ducts and increased sodium absorption in principle cells containing ducts. Moreover, the liquid at the terminal renal ducts is electrically negative, so secretion of hydrogen ions to the duct cavity and liquid absorption of bicarbonate from the renal ducts are also increased. Besides, hypoaldosteronism may cause high K^+ and Cl^--mediated acidosis in the body, which was offset by insufficient intake and excessive consumption in patients with COVID-19. As a result, the patient's plasma K^+, Na^+ and Cl^- were able to remain within the normal range, and none of the patients had severe ventricular arrhythmias. Nevertheless, metabolic alkalosis still occurs when COVID-19 patients had severe hypoxia and insufficient tissue perfusion, even when plasma K^+, Na^+ and Cl^- are within the normal range. Without treatment in time, death may occur after vicious cycles of tissues and organs with severe hypoxia and metabolic alkalosis [22].

For severe metabolic alkalosis treatment, ammonium chloride and other acidic drugs are committed to the restoration of extracellular fluid capacity. However, due to the lack of K^+, the renal duct cells continue to exchange Na^+ with a large number of H^+. Thus, HCO_3^- cannot be excreted, and alkalosis still cannot be corrected. Besides, in the restoration of extracellular fluid capacity, the excessive sodium-containing liquid will increase the charge of H^+ and K^+, resulting in potassium deficiency and more severe alkalosis. To correct alkalosis, supplementation of potassium can rescue intracellular potassium deficiency and increase the chance of HCO_3^- excretions. Instead of ammonium chloride or arginine hydrochloride, severe metabolic alkalosis can be treated with the administration of isotonic hydrochloride solution through the central venous catheter. Patients with metabolic alkalosis are mostly deficient in body fluid, so their total body fluid volume is calculated as 50% of their body weight. Meanwhile, both groups showed AB values higher than SB values, and SB values in the diabetes group were significantly higher than those in the NGT group, suggesting that patients with severe COVID-19 had mixed acid-base balance disorders. This will make conditions more complicated and intense when combined with T2D.

Critically ill patients often have hypocalcemia, and the severity is negatively correlated with the plasma calcium concentration [33, 34]. Metabolic alkalosis may also cause a decrease in blood calcium levels, leading to hand and foot convulsions [35]. In this study, serum Ca^{2+} and P^{3+} of patients are all under the lower limit of normal, and PO_2 is positively correlated with serum Ca^{2+} and P^{3+}. In 23 patients, 12 (52.17%) of the patients experienced hand and foot convulsions, suggesting that hypocalcemia is vital for the severity of lung damage in COVID-19 patients.

Given that the low calcium of diabetic patients is severer than that of non-diabetic patients, the risk of death in diabetic patients would be higher. Therefore blood calcium examination is also critical and should not be ignored. To improve the treatment, timely detection of blood gas and plasma K^+, Na^+, Cl^-, Ca^{2+} and P^{3+} level is essential to assess the severity after the clinical diagnosis. Additional therapeutic management, such as supplementation of calcium, should also be considered to improve the metabolic alkalosis if necessary.

In this study, all patients with severe COVID-19 in general wards underwent standard antiviral treatment as described, and took high-flow oxygen therapy (oxygen absorption concentration of 30-85%) due to extensive lung damage [36]. In the diabetes group, patients also had comorbidities, such as hypertension (81.82%), coronary heart disease and arterial sclerosis in the aorta (27.27%). Of note, patients with T2D had a microcirculation disorder caused by chronic hyperglycemia, and this may further exacerbate pulmonary ischemic hypoxia when combined with severe COVID-19. It is also reported that high-flow oxygen therapy significantly reduced the mortality of patients with severe pneumonia compared with noninvasive ventilation [37].

Conclusion

In this study, the arterial blood lactic acid level in patients with severe COVID-19 was significantly higher than normal on average, and blood lactic acid was negatively correlated with pH. Severe lung damage in patients with severe COVID-19 can lead to severe hypoxemia with the emergence of metabolic alkalosis. It should be noted that severer metabolic alkalosis was presented in T2D patients, which masked the metabolic acidosis due to abnormal sugar metabolism and lactic acid accumulation. The condition becomes severer with enormous uncertainty and difficulty to assess prognosis when combined with T2D and the high-flow oxygen therapy that may have a risk of respiratory alkalosis. A timely examination should be performed for blood gas and electrolytes analysis (i.e. K^+, Na^+, Cl^-, Ca^{2+}, and P^{3+}).

The possibility of mixed acid-base disturbances cannot be ruled out even if pH, K^+ and Cl^- are normal. To take timely and effective treatment for patients with T2D complicated with severe COVID-19, a comprehensive analysis of respiratory and metabolic factors for primary disease's influence should be performed to assess the disease's severity. Although only a small number of patients were included and evaluated in the study, our findings still provide an efficient indicator for treating T2D diabetic patients with severe COVID-19.

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Disclosure of conflict of interest

None.

Abbreviations

COVID-19, Coronavirus disease 2019; T2D, Type 2 diabetes; NGT, normal glucose tolerance; SB, serum bicarbonate; AB, actual bicarbonate; BE, blood alkaline excess; BEecf, base excess in the extracellular fluid Compartment; PO_2, partial pressure of oxygen; ALT, alanine transaminase; AST, aspartate transaminase; TG, triacylglycerol; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SO_2, oxygen saturation; LA, lactic acid; WHO, World Health Organization.

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