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ORIGINAL RESEARCH

Hyperosmolarity Deserves More Attention in Critically Ill COVID-19 Patients with Diabetes: A Cohort-Based Study

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Purpose: Recently, a cluster of pneumonia caused by SARS-CoV-2 were identified in Wuhan and spread throughout the world. More information about risk factors for mortality of critically ill patients infected with SARS-CoV-2 remain to be evaluated.

Methods: We included adult patients confirmed with SARS-CoV-2 infection who were critically ill and admitted to the intensive care unit (ICU) of Tongji Hospital in Wuhan from Feb 4, 2020 to Feb 20, 2020. Data were collected and compared between patients who died and improved. Logistic regression was used to explore the risk factors for death of SARS-CoV-2-infected critically ill patients.

Results: A total of 160 critically ill patients with SARS-CoV-2 infection were included, of which 146 patients with appeared outcomes were included into the final analysis. The random blood glucose, serum sodium and effective plasma osmolarity were higher in deceased patients, especially in patients with diabetes. There were 7 patients with diabetes with hyperosmolar status and all of them were deceased. Multivariable regression revealed that older age (odds ratio 4.28, 95% CI 1.01–18.20; p = 0.049), higher C-reactive protein (odds ratio 1.01, 1.00–1.03; p = 0.024), higher interleukin-6 (odds ratio 1.01, 1.00–1.03; p = 0.0323), and d-dimer greater than 1 μg/mL (odds ratio 1.10, 1.01–1.20; p = 0.032) at admission were associated with increased odds of death.

Conclusion: In conclusion, hyperosmolarity needs more attention and may contribute to mortality in critically ill patients with COVID-19, especially in those with diabetes. Older age, inflammatory response, and thrombosis may be risk factors for death of critically ill patients with SARS-CoV-2 infection.

Keywords: SARS-CoV-2, critically ill, hyperosmolarity, diabetes, risk factors, mortality

Introduction

In early December 2019, the first pneumonia cases of unknown cause were identified in Wuhan, Hubei province in China.[1] A novel betacoronavirus, that is currently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the pathogen through high-throughput sequencing of respiratory tract samples of patients.[2,3] Several evidences pointed out that SARS-CoV-2 has caused person-to-person transmission all over the world.[4–8]

The coronavirus disease 2019 (COVID-19) has already spread rapidly to most parts of China as well as around the world, which has been declared as a pandemic by the World Health Organization (WHO).[9] COVID-19 is more likely to develop to a critically ill level and has caused higher mortality especially in patients with

metabolic disorders (diabetes, obesity, hypertension, etc).[10–12] The clinical spectrum of COVID-19 ranges from mild to critically ill cases. Previous studies have described the general clinical features of patients infected with SARS-CoV-2, including epidemiological, clinical, laboratory, radiological characteristics, treatment, and outcomes.[1,11,13–16] At present, controlling the morbidity of critically ill cases and reducing mortality still remain a great challenge for COVID-19.[17] However, the clinical information characterizing critically ill patients was insufficient. One study has described the clinical course and outcomes of 52 critically ill patients with confirmed COVID-19 who were admitted to the intensive care unit (ICU) of Wuhan Jin Yin-tan hospital (Wuhan, China).[18] COVID-19 is becoming increasingly severe in other countries and regions outside China, Therefore, comprehensive analysis of data from different centers is necessary to ultimately establish treatment guidelines and risk score for COVID-19. An updated analysis to investigate critically ill patients confirmed with SARS-CoV-2 infection will be of vital importance to reduce mortality.

Serum osmolarity, which depends on the concentrations of Na^+, K^+, Cl^-, glucose and urea, plays an important role in various body fluid balances.[19] Perturbation of serum osmolarity is associated with clinically adverse outcomes. The association between hyperosmolarity and mortality has been studied in several diseases, such as patients with acute coronary syndrome,[20] intracranial hemorrhage,[21] stroke,[22] acute pulmonary embolism[23] as well as in critically ill patients,[24] the results showed that hyperosmolarity is associated with increased mortality. Additionally, as an acute complication of diabetes, hyperosmolarity is strongly associated with poor outcome or mortality in patients with severe hyperglycemic crisis. For COVID-19, whether hyperosmolarity plays a predictive role in mortality in critically ill patients still remains unclear.

In this study, we investigated critically ill patients with confirmed SARS-CoV-2 pneumonia who were admitted to the ICU of Tongji hospital in Wuhan. We aim to describe the epidemiological, clinical, laboratory, treatment, and outcomes, and to explore the risk factors for death in critically ill patients with COVID-19.

Methods

Study Design and Participants

The patients or their authorized person in this study were informed about the purpose of the study, that verbal informed consent was approved by the Institutional Ethics Board of Tongji Hospital, Huazhong University of Science and Technology (No. TJ-IRB20200315), and that this study was conducted in accordance with the Declaration of Helsinki. This retrospective, observational study was done at Tongji Hospital in Wuhan (China), which is the designated hospital for treatment for COVID-19. All patients with COVID-19 enrolled in this study were confirmed with SARS-CoV-2 infection by PCR according to World Health Organization interim guidance.[25] We enrolled patients admitted to ICU in Tongji Hospital from Feb 4, 2020 to Feb 20, 2020. Among them, 146 had appeared outcomes and were included in the final analysis after excluding 14 other patients (13 were still hospitalized and 1 was transferred). Critically ill patients were defined as those admitted to the ICU who required mechanical ventilation or had a fraction of inspired oxygen (FiO2) of at least 60% or more as previously described.[18] The clinical outcomes (ie, dead, improved, still hospitalized in ICU) were monitored up to March 11, 2020, the final date of follow-up. The study flow diagram is shown in Figure 1.

Data Collection

We collected clinical medical records, nursing records, and laboratory findings for all patients with laboratory confirmed COVID-19 with standardized data collection forms. The data were reviewed by a trained team of physicians. We collected data on age, sex, medical history, smoking history, chronic comorbidities (hypertension, chronic cardiac disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, cancer, and diabetes), symptoms from onset to hospital admission (fever, the highest temperature, cough, expectoration, dyspnoea, chest pain, diarrhea, nausea, vomiting, poor appetite, myalgia, headache, and fatigue), vital signs at hospital admission (temperature, blood pressure, heart rate, respiratory rate and oxygen saturation), laboratory tests on hospital admission and treatments (antiviral therapy, Chinese patent medicine, antibiotics therapy, corticosteroid, mechanical ventilation and life support).

Definitions

The laboratory abnormalities were according to the normal value range of the clinical laboratory in Tongji Hospital. Diabetic ketoacidosis, acute kidney injury, rhabdomyolysis, and disseminated intravascular coagulation were defined by clinicians according to the clinical

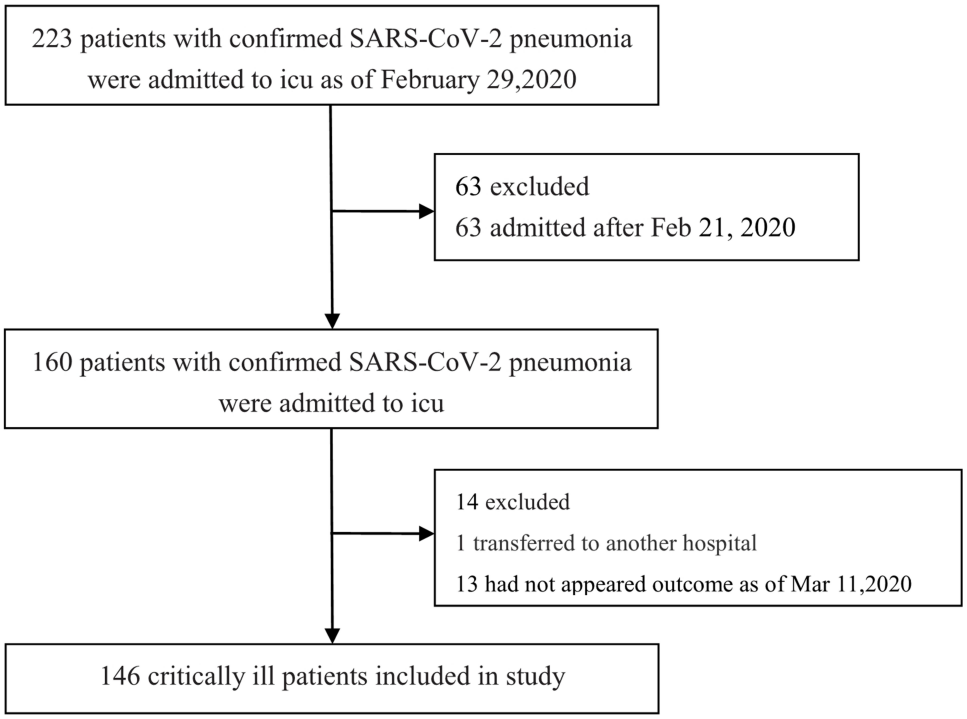

Figure 1 Study flow diagram.

guideline.[26–28] Cardiac injury was defined if the serum high sensitivity cardiac troponin I (cTnI) was above 131 pg/mL. Hepatic dysfunction was defined if alanine transaminase (ALT) was above 3 folds of the upper limit of normal. The effective plasma osmolarity was calculated by (sodium (mmol/L) + potassium (mmol/L)) *2 + random blood glucose (mmol/L), the estimated plasma osmolarity above 320 mOsm/L was defined as hyperosmolarity. The collected laboratory tests were on hospital admission.

Statistical Analysis

Continuous variables were described as the medians and interquartile ranges (IQR). Categorical variables were expressed as the frequency and its percentages in each group. According to their outcomes, we eliminated the cases that had no apparent outcome yet and grouped the remaining cases into improvement or death to compare their differences. When the data was normally distributed, independent group *t*-tests were used for continuous variables; otherwise, Wilcoxon rank-sum tests were applied. While chi-square tests and Fisher's exact tests were applied to categorical variables as appropriate. To analyze the odds ratios of death versus improvement among ICU cases and the potential risk factors, we fitted a logistic regression model. The candidate risk factors included gender, age, laboratory findings and the development of complications. Firstly, we incorporated a single candidate variable from those candidate risk factors into the univariate models orderly. Then, the statistically significant risk factors in univariate models were included into the final models. All analyses were conducted with SAS software version 9.4. The forest figure was plotted using R software version 3.6.3.

Results

Demographic and Clinical Characteristics

The study population included 160 patients with COVID-19 who had been hospitalized in the ICU of Tongji Hospital, and obtained data regarding clinical symptoms and outcomes. Among them, 146 with appeared outcomes were included into the final analysis (27 patients improved and 119 died during hospitalization), 13 were still hospitalized and 1 was transferred. The median durations from onset to hospital admission and ICU admission were 10 days (IQR, 7–15), 14 days (IQR, 10–19) respectively (Supplemental Table 1). The median durations from ICU admission to death or improvement were 7 days (IQR, 3–12) or 9 days (IQR, 7–20) respectively. Compared with the death group, the median time from admission to ICU for the improved group is shorter ($Z = -2.7294$, $P<0.05$), which were 2 days (IQR, 0–5) and 0 day (IQR, 0–3) respectively (Supplemental Table 1).

Of the 146 patients, the median age was 69 years (IQR, 59–76; range, 22–92 years), and 61.6% of the patients were men. Patients who died were older than those who improved by a median of 15 years. The demographic and clinical characteristics of the patients are shown in Table 1 and Figure 2. The most common symptoms at onset of illness were fever (127 [88.8%]), dyspnea (112 [78.3%]), cough (110 [76.9%]), fatigue (69 [48.6%]), and poor appetite (65 [45.8%]). Less common symptoms were headache, chest pain, diarrhea, nausea, and vomiting (Supplemental Table 2). Dyspnea was more common in patients who died than in the improved group. Among the overall population, hypertension (69 [49.3%]) was the most common chronic coexisting condition. Acute complications among the 146 patients included poor liver function (57 [40.1%]), myocardial injury (47 [34.3%]), hyperuricemia (27 [19.0%]), and hypernatremia (24 [17.0%]) (Table 1).

On admission to hospital, temperature, pulse, respiratory rate, and blood pressure did not differ between patients who died and patients with improved. The blood oxygen saturation of the death group was significantly lower than that of the improved group (t=3.0052, P< 0.05) (Supplemental Table 2). Compared with patients who improved (n = 27), patients who died (n = 119) had more dyspnea (Supplemental Table 2) and higher random blood glucose (8.32 [6.55~12.38] vs 7.05 [5.49~9.50], P = 0.043) (Table 2), and were more likely to have underlying comorbidities, like myocardial damage (44 [39.6%] vs 3 [11.5%], P = 0.007) (Table 1). The result also showed the comorbidities, such as hypertension (58 [50.4%] vs 11 [44.0%]), chronic pulmonary disease (11 [9.6%] vs 0 [0%]), and cardiovascular disease (25 [21.7%] vs 4 [16.7%]) were more common in the death group, although this difference was not statistically significant (Table 1). The death group was more likely to have one of these complications than improved patients.

Table 1 Baseline Characteristics of 146 Critically Ill Patients with COVID-19

	All Patients(n=146)	Death(n=119)	Improvement(n=27)	*P* value[a]
Age years	69(59～76)	70 (62～78)	55 (36～71)	<0.001
Distribution				
<65	54(37.0)	38(31.9)	16(59.3)	0.008
≥65	92(63.0)	81(68.1)	11(40.7)	
Sex				
Male	90(61.6)	76(63.9)	14(51.9)	0.246
Female	56(38.4)	43(36.1)	13(48.1)	
Smoking history	15(11.4)	13(11.8)	2(9.1)	>0.99
Chronic coexisting disorders				
Hypertension	69(49.3)	58(50.4)	11(44.0)	0.560
Cardiovascular disease	29(20.9)	25(21.7)	4(16.7)	0.578
Cerebrovascular diseases	9(6.5)	7(6.1)	2(8.3)	>0.99
Chronic pulmonary disease	11(7.9)	11(9.6)	0(0)	0.245
Chronic renal diseases	5(3.6)	3(2.6)	2(8.3)	0.206
Chronic liver disease	5(3.6)	5(4.3)	0(0)	0.587
Cancer	4(3.4)	3(3.1)	1(4.3)	0.582
Diabetes	48(33.8)	40(34.2)	8(32.0)	0.834
Acute coexisting disorders				
Hepatic dysfunction	57(40.1)	49(42.2)	8(30.8)	0.281
Hypernatremia	24(17.0)	23(20.0)	1(3.8)	0.996
Hyperuricemia	27(19.0)	23(19.8)	4(15.4)	0.806
Myocardial damage	47(34.3)	44(39.6)	3(11.5)	0.007
Rhabdomyolysis	1(0.7)	1(0.8)	0(0)	>0.99
Acute kidney injury	3(2.1)	3(2.5)	0(0)	>0.99
Disseminated intravascular coagulation	1(0.7)	1(0.8)	0(0)	>0.99

Notes: Data are presented as n (%) or median (interquartile range), unless otherwise stated; [a]P values indicate differences between death and improvement; P<0.05 was considered statistically significant.

Abbreviations: COVID-19, the coronavirus disease 2019; bpm, beats per minute.

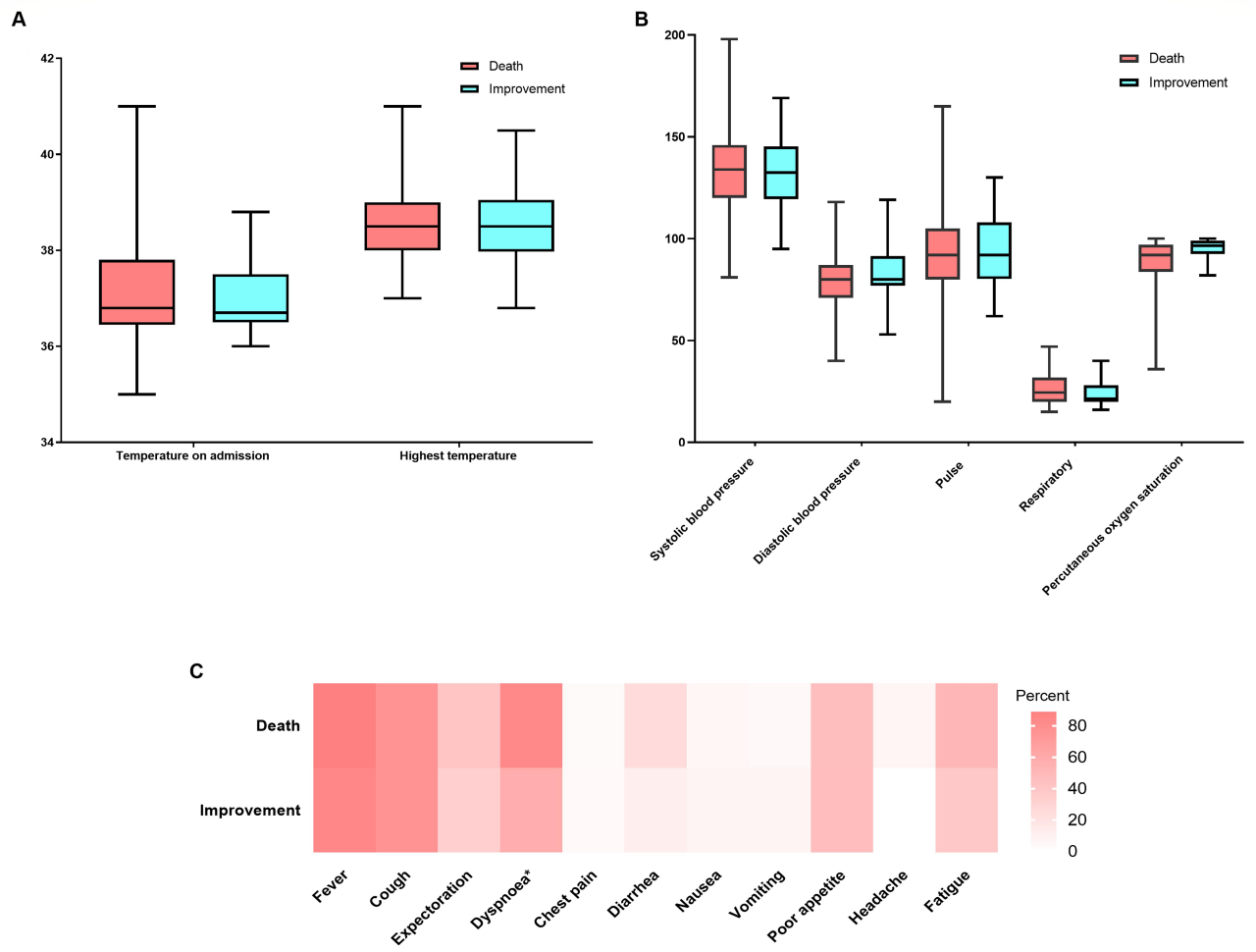

Figure 2 Clinical symptoms and signs of 146 critically ill patients with COVID-19. (**A** and **B**) The average (with standard deviation) of clinical signs in the death and the improvement. (**C**) Percentage of each clinical symptom in the death and the improvement. *Represents P<0.05.

Factors Associated with Plasma Osmolarity

We were especially concerned with the factors contributing to plasma osmolarity shown in Table 2. The reference range of laboratory findings were listed in Supplemental Table 5. Compared with patients who improved (n = 27), patients who died (n = 119) had higher sodium, blood glucose, and effective plasma osmolarity. In the subgroup of diabetes, the sodium and effective plasma osmolarity were higher in the death group, and the difference of effective plasma osmolarity were more marked. But there was no difference of blood glucose between deaths and survivors in patients with diabetes (Table 2, Figure 3 and Supplemental Table 3). Besides, there were 7 patients with diabetes with hyperosmolar status and all of them died. There was no difference of diabetes ketoacidosis in the death group and improved group (Table 2).

Laboratory Parameters and Treatment

The laboratory tests of the patients on admission are shown in Table 3. There were numerous differences in laboratory tests between the improvement group and the death group. Patients from the death group had more significant laboratory abnormalities, including higher levels of lactic dehydrogenase, total protein, d-dimer, C-reactive protein (CRP), serum ferritin, high sensitivity cTnI, interleukin-2 receptor (IL-2R), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10) and brain natriuretic peptide level (BNP), as well as lower lymphocyte count, platelet count, estimated glomerular filtration rate (eGFR), actual bicarbonate (AB) and total cholesterol level.

Table 2 Factors Associated with Plasma Osmolarity of 146 Critically Ill Patients with COVID-19

	All	Death	Improvement	*P* value[a]
All patients, counts	**146**	**119**	**27**	
Hyperosmolar status	7(5.1)	7(6.3)	0(0.0)	0.350
Diabetes ketoacidosis	2(1.5)	1(0.9)	1(4.0)	0.333
Potassium mmol·L^{-1}	4.39(3.88～4.82)	4.38(3.78～4.83)	4.44(4.17～4.82)	0.458
Sodium mmol·L^{-1}	139.20(136.20～143.20)	139.70(136.40～144.00)	138.25(135.30～139.50)	0.034
Random blood glucose mmol·L^{-1}	7.94(6.31～11.73)	8.32(6.55～12.38)	7.05(5.49～9.50)	0.043
Plasma osmolarity mOsm/L	296.47(290.31～305.26)	298.32(290.50～ 308.37)	293.23(289.74～ 296.82)	0.033
Patients with diabetes, counts	48	40	8	
Hyperosmolar status	7(14.9)	7(17.9)	0(0.0)	0.329
Diabetes ketoacidosis	2(4.3)	1(2.6)	1(12.5)	0.315
Potassium mmol·L^{-1}	4.43(3.91～ 4.89)	4.48(3.91～ 4.89)	4.38(3.86～ 5.01)	0.729
Sodium mmol·L^{-1}	139.60(136.05～ 145.95)	142.10(137.55～ 149.20)	136.85(134.50～ 139.05)	0.046
Random blood glucose mmol·L^{-1}	14.67(11.31～ 18.17)	14.83(11.77～ 18.53)	12.46(10.13～ 16.99)	0.313
Plasma osmolarity mOsm/L	303.86(296.00～ 319.15)	308.97(297.11～ 324.33)	296.20(292.86～ 296.67)	0.013

Notes: Data are presented as n (%) or median (interquartile range), unless otherwise stated; [a]P values indicate differences between death and improvement, P<0.05 was considered statistically significant.
Abbreviation: COVID-19, the coronavirus disease 2019.

The treatment of the 146 critically ill patients is shown in Table 4. A majority of the patients (97.2%) received antibiotic therapy, 82.6% received antiviral therapy, and 87.1% received corticosteroid therapy; non-surviving patients received higher doses of corticosteroid. Most patients (67.6%) received endotracheal intubation, and higher percentages of non-surviving patients received this therapy. Patients in the improvement group were more likely to receive nasal catheter oxygen inhalation than those in the death group. Of all critically ill patients with COVID-19, few received high-flow oxygen (2.1%) and extracorporeal membrane oxygenation (2.1%). More patients in the dead group received replacement therapy than in the improved group (26 [21.8%] vs 2 [7.7%]).

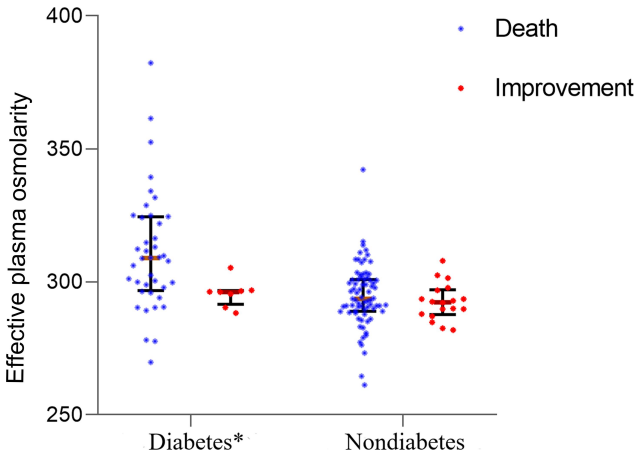

Figure 3 The plasma osmolarity of 146 critically ill patients with COVID-19. The median (interquartile range) of plasma osmolarity in patients with or without diabetes. *Represents P<0.05.

Risk Factors for Mortality in Patient with COVID-19

In univariable analysis, the odds of in-ICU death was higher in patients with dyspnea (Supplemental Table 4). Age, dyspnea, lymphopenia, reduced eGFR and oxygen saturation, increased CRP, prothrombin time (PT), d-dimer, IL-6 and serum ferritin, were also associated with death.

Based upon the above results, we included 114 patients with complete data for all variables (25 improved and 89 died) in the multivariable logistic regression model. We found that older age, higher CRP, IL-6, and a d-dimer greater than 1 μg/mL at admission were associated with increased odds of death (Figure 4).

Correlation Among Osmolarity and the Inflammatory Markers

In addition, we analyzed the correlation relationship between osmolarity and inflammatory markers (Supplemental Table 6). The results showed that the lymphocyte count (r = −0.1831, P = 0.0309), lactic dehydrogenase (r = 0.3439, P<0.0001), total bilirubin (r = 0.4017, P<0.0001), d-dimer (r = 0.2226, P = 0.0089), interleukin-6 (r = 0.3398, P = 0.0002), interleukin-8 (r

Table 3 Laboratory Findings of 146 Critically Ill Patients with COVID-19

	All Patients(n=146)	Death(n=119)	Improvement(n=27)	*P* value[a]
White-cell count $\times10^9\cdot L^{-1}$	8.96(6.17～13.08)	9.15(6.15～13.35)	7.89(6.17～10.66)	0.245
Neutrophil count $\times10^9\cdot L^{-1}$	7.85(4.90～11.60)	8.10(5.38～12.02)	5.81(4.61～9.69)	0.107
Lymphocyte count $\times10^9\cdot L^{-1}$	0.58(0.43～0.86)	0.56(0.43～0.80)	0.79(0.49～1.12)	0.023
Monocyte count $\times10^9\cdot L^{-1}$	0.39(0.25～0.60)	0.37(0.23～0.55)	0.47(0.28～0.87)	0.092
Eosinophil count $\times10^9\cdot L^{-1}$	0.00(0.00～0.02)	0.00(0.00～0.01)	0.03(0.00～0.09)	<0.001
Erythrocyte count $\times10^{12}\cdot L^{-1}$	4.12(3.71～4.54)	4.16(3.83～4.55)	3.80(3.56～4.45)	0.105
Haemoglobin level $g\cdot L^{-1}$	129.0 (116.0～141.0)	131.5 (117.0～142.5)	120.5(108.0～138.0)	0.062
Platelet count $\times10^9\cdot L^{-1}$	161.0(118.0～234.0)	151.0(108.0～223.0)	202.0(152.0～317.0)	<0.001
Alanine transaminase $U\cdot L^{-1}$[b]	29.5(19.0～46.0)	29.0(19.0～43.5)	34.5(20.0～65.0)	0.288
Aspartate aminotransferase $U\cdot L^{-1}$[b]	40.5(26.0～63.0)	43.5(29.5～63.5)	32.5(22.0～47.0)	0.101
Lactic dehydrogenase $U\cdot L^{-1}$[b]	506.5(376.0～695.0)	540.0(422.5～742.0)	361.0(282.0～485.0)	0.009
Creatine kinase $U\cdot L^{-1}$[b]	133.5(70.0～354.0)	133.5(73.0～356.0)	127.0(36.5～239.0)	0.075
Total bilirubin $\mu mol\cdot L^{-1}$	13.25(8.50～19.20)	13.90(9.80～20.60)	8.85(7.20～14.40)	0.007
Albumin $g\cdot L^{-1}$	31.00(27.50～33.80)	30.80(27.35～33.40)	31.35(27.80～35.60)	0.057
eGFR $mL\cdot min^{-1}$	76.01(52.47～94.09)	71.98(48.74～90.63)	94.95(73.74～116.95)	<0.001
Actual bicarbonate $mmol\cdot L^{-1}$	21.50(18.80～ 24.10)	20.90(18.60～23.90)	23.25(21.90～25.25)	0.007
Uric Acid $\mu mol\cdot L^{-1}$	259.55(181.00～373.00)	261.55(184.00～378.50)	219.00(165.00～364.00)	0.367
Total Cholesterol $mmol\cdot L^{-1}$	3.35(2.90～3.97)	3.33(2.75～3.87)	3.67(3.16～4.49)	0.006
Triglyceride $mmol\cdot L^{-1}$	1.56(1.20～2.23)	1.57(1.22～2.23)	1.48(1.18～2.34)	0.681
Glycosylated hemoglobin $mmol\cdot L^{-1}$	6.45(6.15～6.80)	6.50(6.20～6.90)	6.40(6.00～6.60)	0.347
Calcium $mmol\cdot L^{-1}$	2.08(2.00～2.19)	2.07(1.98～2.15)	2.17(2.05～2.24)	0.024
Prothrombin time s	15.4(14.4～17.3)	15.6(14.6～17.7)	14.5(13.8～15.5)	0.002
D-dimer $mg\cdot L^{-1}$	6.89(1.74～21.00)	10.46(2.12～21.00)	2.26(1.02～6.71)	0.002
C-reactive protein $mg\cdot L^{-1}$	97.20(47.30～142.10)	107.30(60.70～150.50)	44.65(19.00～91.90)	<0.001
Erythrocyte sedimentation rate $mm\cdot H^{-1}$	36(20～62)	35(19～59)	53(28～72)	0.175
Procalcitonin $ng\cdot mL^{-1}$	0.20(0.10～0.66)	0.20(0.11～0.67)	0.14(0.06～0.26)	0.034
Serum ferritin $\mu g\cdot L^{-1}$	1294.2(856.5～2290.4)	1352.1(969.9～2412.4)	825.3(643.4～1555.9)	0.007
Brain natriuretic peptide $pg\cdot mL^{-1}$	804.5(226.0～2545.0)	945.0(362.0～2636.0)	155.5(75.0～852.0)	<0.001
Cardiac troponin I $pg\cdot mL^{-1}$	31.15(9.45～271.15)	48.70(12.10～471.20)	6.60(2.60～19.50)	<0.001
Interleukin-1β $pg\cdot mL^{-1}$	5.00(5.00～5.00)	5.00(5.00～5.00)	5.00(5.00～5.00)	0.258
Interleukin-2R $U\cdot mL^{-1}$	1092.00(772.00～1565.00)	1170.00(884.00～1583.00)	931.00(581.00～1111.00)	0.025
Interleukin- 6 $pg\cdot mL^{-1}$	51.39(22.28～137.35)	68.00(29.42～164.40)	22.45(7.60～31.76)	<0.001
Interleukin- 8 $pg\cdot mL^{-1}$	26.10(15.50～56.00)	32.25(17.55～69.50)	17.80(10.50～23.40)	<0.001
Interleukin- 10 $pg\cdot mL^{-1}$	8.90(5.40～14.90)	10.10(5.70～15.60)	6.10(5.00～8.90)	0.027
Tumor Necrosis Factor-α $pg\cdot mL^{-1}$	10.70(7.70～17.50)	11.30(8.00～18.30)	9.80(6.80～14.60)	0.130

Notes: Data are presented as median (interquartile range), unless otherwise stated; Reference range for above laboratory findings were provided in supplementary materials (Supplemental Table 5); [a]P values indicate differences between death and improvement, P<0.05 was considered statistically significant; [b]SI conversion factors, to convert alanine transferase to μkat/L, multiply by 0.0167; aspartate aminotransferase to μkat/L, multiply by 0.0167; creatine kinase to μkat/L, multiply by 0.0167; and lactate dehydrogenase to μkat/L, multiply by 0.0167.

Abbreviation: COVID-19, the coronavirus disease 2019.

= 0.2450, P = 0.008), and tumor necrosis factor-α (r = 0.4065, P =< 0.0001) were significantly correlated with osmolarity.

Discussion

This retrospective study reported clinical features of 146 critically ill patients (with 27 who improved and 119 who died) who were confirmed as having the SARS-CoV-2 infection. Importantly, plasma hyperosmolarity may contribute to the death rates of critically ill patients with COVID=19. Besides, older age, higher CRP, IL-6, and a d-dimer greater than 1 μg/mL at admission were associated with higher odds of in-ICU death.

Importantly, the random blood glucose was higher in the dead group than the improved group. Zhou et al reported that odds of in-hospital death was higher in patients with diabetes[29] and the blood glucose needed better management in patients with COVID-19.[30] The random blood glucose, serum sodium and effective plasma osmolarity were higher in deceased patients than in improved patients, which suggestiions that plasma hyperosmolarity may be associated

with higher mortality. Additionally, the sodium levels were not significant in both univariate and multivariate analysis. A consistent association between hyponatremia and increased mortality has been shown in different hospitalized patients.[31–33] The osmolarity mainly depends on Na^+, K^+, Cl^-, glucose and urea. The results in this study indicate that in critically ill patients with COVID-19, blood sodium may not be the main cause in the increased osmolarity. We may need a comprehensive management for all components of osmolarity to improve the outcome of COVID-19. The hyperosmolar status in patients with diabetes did not show a significant difference between the dead and improved group. Specifically, there were 7 patients with diabetes with hyperosmolar hyperglycemia syndrome and all of them were deceased. Meanwhile, there were 2 patients with diabetic ketoacidosis, of which 1 died and another was improved. The results suggest that hyperosmolar status in diabetes but not diabetic ketoacidosis seems to be associated with a higher risk of death in critically ill patients with COVID-19 despite the hyperosmolar status failing to reach a significant statistical difference, which may be due to the limited sample size in this study. In the subgroup of patients with diabetes, the estimated effective plasma osmolarity was also higher in the dead group than in the improved group. As the poor management of blood glucose would aggravate the hyperosmolar status in patients with diabetes, thus increasing the risk for death. It is known that serum osmolarity plays an important role in body fluid balances, while perturbation of serum osmolarity is strongly associated with internal environment disorder, such as dehydration and hypernatremia which may lead to a poor clinical outcome.[19] It is reported that hyperosmolarity is associated with increased mortality in various diseases.[20–24,34] First, hyperosmolarity is always accompanied by the increase of its main components, such as hyperglycemia, hypernatremia or hyperkalemia, which have been reported as risk factors for cardiac mortality.[35,36] Second, hyperosmolarity could cause the redistribution of body fluids, such as transport of fluids from interstitial space to the effective circulation, thus increasing the preload of cardiac and leading to poor outcomes, such as heart failure and malignant arrhythmia.[24] In this study, we found no significant difference of hyperosmolarity in the mortality of COVID-19 patients after multivariate analysis. This may be because of the limited sample size or the heterogeneity between patients with COVID-19 and patients with other diseases. Further studies are needed to explore the importance of hyperosmolarity in COVID-19 related mortality. These results suggest the importance of early identification and treatment of plasma hyperosmolarity in critically ill patients with COVID-19, especially in patients with diabetes.

Until now, no specific treatment has been identified to treat SARS-CoV-2. Currently, the dominant therapies for COVID-19 are antivirus, Chinese patent medicine, antibiotics, corticosteroids and other non-drug supportive treatments. About 82% patients in this study received antiviral therapy, 43% received Chinese patent medicine,

Table 4 Treatment of 146 Critically Ill Patients with COVID-19

	All Patients(n=146)	Death(n=119)	Improvement(n=27)	*P* value[#]
Drug therapy				
Antiviral therapy	114(82.6)	95(83.3)	19(79.2)	0.847
Chinese patent medicine	54(43.9)	43(42.6)	11(50.0)	0.525
Antibiotics therapy	138(97.2)	114(97.4)	24(96.0)	0.543
Corticosteroid	122(87.1)	104(89.7)	18(75.0)	0.106
Corticosteroid dose Median (IQR) mg	40(40～80)	40(40～80)	40(0～80)	0.042
<40	80(57.1)	63(54.8)	17(68.0)	0.087
40–80	46(32.9)	38(33)	8(32.0)	
>80	14(10)	14(12.2)	0(0)	
Non-drug Therapy				
Nasal catheter oxygen inhalation	17(11.7)	3(2.5)	14(53.8)	<0.001
High-flow oxygen	3(2.1)	0(0)	3(11.5)	0.005
BiPAP	27(18.6)	25(21)	2(7.7)	0.193
Endotracheal intubation	98(67.6)	91(76.5)	7(26.9)	<0.001
Extracorporeal membrane oxygenation	3(2.1)	3(2.5)	0(0)	>0.99
Replacement therapy	28(19.3)	26(21.8)	2(7.7)	0.098

Notes: Data are presented as n (%), unless otherwise stated; [#]P values indicate differences between death and improvement, P<0.05 was considered statistically significant.
Abbreviations: COVID-19, the coronavirus disease 2019; IQR, interquartile range.

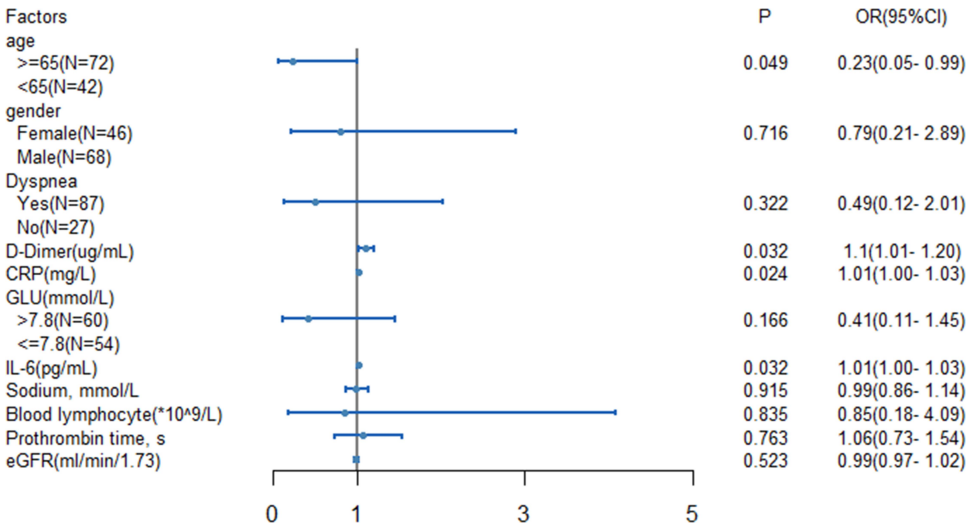

Figure 4 The risk factors for death in critically ill patients with COVID-19. Shown are the stratification by age, gender, dyspnea, random blood glucose (GLU), and interleukin-6 (IL-6), serum sodium, blood lymphocyte, percutaneous oxygen saturation (spo2), estimated glomerular filtration rate (eGFR), d-Dimer, C-reactive protein (CRP).

and 97% received antibiotics therapy. At present, no antiviral agents were found to provide a benefit for the outcome of COVID-19. For critically ill patients with a virus infection, corticosteroids were often used to reduce inflammatory-induced lung injury. However, cumulative evidences suggest that corticosteroids did not have effect on mortality in patients with SARS-CoV and MERS-CoV, but rather delayed the virus clearance.[37,38] In this study, about 87% of critically ill patients with COVID-19 received corticosteroid therapy. The number of patients who received corticosteroid was more in the death group than for those who improved. Despite the fact that 1–2 mg/kg/d corticosteroid was recommended for critically ill patients in the 7th guideline for COVID-19 in China, no improved patients were observed in those received more than 80 mg/d methylprednisolone sodiumsuccinate in this study, suggesting the dose of corticosteroid of more than 80 mg/d may exhibit no improved effect on outcome of COVID-19. Corticosteroid therapy is often accompanied by elevated blood glucose and sodium storage, which may exacerbate the plasma osmolarity. Therefore, physicians should be more cautious of the corticosteroid therapy in patients with diabetes. Inconsistently, a recent study by researchers from the RECOVERY clinical trial found that dexamethasone reduced 28-day mortality. The benefit was greatest in patients who received either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support.[39] Meanwhile, another research observed that intravenous dexamethasone resulted in a significant increase in the number of ventilator-free days among patients with COVID-19 and moderate or severe ARDS, but there was no significant difference in all-cause mortality at 28 days.[40] The difference may be explained by several factors. First, Wuhan received an early attack by COVID-19, the health care system was confronted with a heavy burden at the early stage of the epidemic. So, the patients enrolled in this study at the initial stage may be more severe than other studies, which exhibited higher mortality than these two studies. Therefore, the benefit of corticosteroids on mortality was not observed in this study. Second, the limited numbers in this study and the heterogeneity between different ethnic groups may be the reason for different results. Third, methylprednisolone sodium succinate was used in this study instead of dexamethasone in other studies. The different physicochemical property of diverse corticosteroids may contribute to the discrepancy in different studies.

Mechanical ventilation and life support are the main supportive treatments for critically ill patients. In this study, about 67% patients received endotracheal intubation, higher percentages of non-surviving patients received this therapy. Some first-line physicians suggest that the endotracheal intubation should be applied before the patients progressed to critically ill to achieve better prognosis. In this cohort, 8 patients received ECMO, of which 3 died and 5 were still hospitalized, which suggests that ECMO might prolong the survival time for critically ill

patients, and the effect of ECMO on the outcome of COVID-19 still needs further investigation.

SARS-CoV-2 can be transmitted directly to humans and has already spread around the world.[5,7] The two highly pathogenic viruses, SARS-CoV and MERS-CoV, have caused severe respiratory syndrome in humans, with a mortality of 10% for SARS-CoV and 37% for MERS-CoV.[41–43] At data cutoff for this study, mortality of the 146 included critically ill patients infected by SARS-CoV-2 was 74%, which was higher than a previous study in critically ill patients.[18] This may be because the cases of previous study were from the early treatment stage of COVID-19, and the cases of current study are from the outbreak stage in which the situation of patients was aggravated.

Our results showed that older age (≥65) was associated with death in ICU patients with COVID-19 and was the greatest risk factor for death, consistent with previous studies.[18,29] The number of men was more than women in patients admitted to ICU in our study. No association between smoking and death outcome was observed in this study. The time from hospital admission to ICU admission was longer in patients who died than those who improved, suggesting timely treatment into ICU may improve the outcome of COVID-19.

The clinical features of COVID-19 were similar with patients presented with SARS-CoV and MERS-CoV infection, which was similar with previous studies.[1,11,13,14,18,29,44,45] Dyspnoea was more common in patients who died in this study, which was the only symptom associated with death. The oxygen saturation was lower in the dead group. This may be because dyspnoea and worse oxygen saturation are usually associated with severe clinical status and delayed treatment. The result suggests the onset of dysponea and hypoxia may predict poor prognosis, timely hospitalization and treatment may improve the outcome.

In terms of laboratory tests, lymphocytopenia was observed in about 84% of critically ill patients in this cohort. Besides, the absolute value of lymphocyte reduced more dramatically in patients who did not survive. The results suggest that SARS-CoV-2 might mainly target lymphocytes, thus damaging the immune system for virus replication. Additionally, lymphocytopenia are also common in critically ill patients with SARS-CoV and MERS-CoV infection.[46,47] Based on previous studies,[13,18,45] the lymphocytopenia was associated with the poor outcome. The eosinophil and platelet counts were also reduced in patients who died than those who improved in the current study. It is reported that eosinopenia was observed in most patients infected with SARS-CoV-2, which correlates positively with lymphocyte counts in severe patients.[48] Platelets are associated with the coagulation function and may be associated with the poor outcome of a SARS-CoV-2 infection, similar to previous studies.[13,14]

The prolonged PT, elevated bilirubin and decreased albumin revealed the dysfunction of liver in critically ill patients, which indicates that hepatic dysfunction may be associated with a high risk for in-ICU death of COVID-19. The d-dimer being greater than 1 μg/mL at admission was a risk factor for the fatal outcome of critically ill patients with COVID-19, consistent with a previous study.[29] In this study, BNP and high sensitivity cTnI were higher in patients who were dead than those who improved, suggesting that acute heart damage may contribute to the poor outcome of patients in ICU with COVID-19.

Virus infection commonly induces cytokine storm to generate immune responses. Patients with cytokine storm progressed rapidly to acute respiratory distress syndrome or septic shock. Therefore, early identification and management of cytokine storm is crucial for critically ill patients with virus infection. SARS-CoV and MERS-CoV infection were reported to induce increased serum proinflammatory cytokines.[49,50] In patients with SARS-CoV-2 infection, the proinflammatory cytokine were increased in recent studies.[1,51] Similarly, the inflammatory factors and cytokines in serum were higher in patients who died than those who improved in this study, which suggests the inflammatory factors and cytokine storm are associated with disease severity and poor outcome. Among all these cytokines, IL-6 and CRP are risk factors for ICU-death.

This study has several limitations. First, information of some cases in this cohort was incomplete, which may affect the results. This is because some patients were too ill to answer questions properly, and it was hard to obtain accurate disease history from these patients. Second, only 146 critically ill patients were included in this study. The limited sample size, especially in the improved group, may make it difficult to assess the risk factors for death in critically ill patients. The non-significant p values should not necessarily rule out a difference between dead and improved patients. Third, at the time of manuscript submission, there are 14 patients still hospitalized and the outcomes are unknown. Additionally, more complete, rigorous, larger clinical studies are needed to uncover the predictive risk factors for death in critically ill patients with COVID-19.

Conclusion

In conclusion, hyperosmolarity needs more attention and may contribute to mortality in critically ill patients with COVID-19, especially in those with diabetes. Older age, inflammatory response (higher C-reactive protein and interleukin-6), and thrombosis (d-dimer greater than 1 μg/mL) at admission may be risk factors for death of critically ill patients with COVID-19.

Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, middle east respiratory syndrome coronavirus; COVID-19, the coronavirus disease 2019; FiO2, fraction of inspired oxygen; IQR, interquartile range; ICU, the intensive care unit; ALT, alanine transaminase; CK, creatine kinase; CRP, C-reactive protein; cTnI, cardiac troponin I; PT, prothrombin time; IL-2R, interleukin-2 receptor; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; TC, total cholesterol; PCT, procalcitonin; ECMO, extracorporeal membrane oxygenation.

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Disclosure

All authors report no conflicts of interest in this work.

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