Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019: a retrospective cross-sectional study

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Posted Date: March 18th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17575/v1

Abstract

Background: To investigate the correlations between serum calcium and clinical severity and outcomes in patients with coronavirus disease 2019 (COVID-19).

Methods: In this clinical retrospective study, the levels of serum calcium, hormone levels and clinical laboratory parameters of admission were recorded. The clinical severity and outcome variables were also recorded.

Results: From February 10 to February 28 2020, 241 patients were enrolled in this study. Of these patients, 180 (74.7%) had hypocalcemia on admission. The median serum calcium levels were 2.12 (IQR, 2.04-2.20) mmol/L, median parathyroid hormone (PTH) levels were 55.27 (IQR, 42.73-73.15) pg/mL, median 25-hydroxy-vitamin D (VD) levels were 10.20 (IQR, 8.20-12.65) ng/mL. The serum calcium levels were significantly positive correlated with VD levels (P =0.004), whereas negative correlated with PTH levels (P = 0.048). Patients with lower serum calcium levels (especially ≤2.0 mmol/L) had worse clinical parameters, higher incidence of organ injury septic shock and higher 28-day mortality. The areas under the receiver operating characteristic curves of multiple organ dysfunction syndrome, septic shock, and 28-day mortality were 0.923 (P <0.001), 0.905 (P =0.001), and 0.929 (P <0.001), respectively. The overall mortality of COVID-19 was 4.1% (10/241), whereas the mortality of critical patients was up to 40.0% (10/25).

Conclusions: Serum calcium was associated with clinical severity and prognosis of patients with COVID-19. Hypocalcemia may be associated with imbalanced VD and PTH.

Key Messages

This was the first study to investigate the correlations between serum calcium and clinical outcomes in patients with COVID-19. We found that patients with serum calcium values ≤ 2.0 mmol/L had higher 28-day mortality, higher incidence of organ injury. The results suggested that redressing of hypocalcemia could be an important strategy to improve the prognosis of patients with COVID-19. Moreover, our study revealed that hypocalcemia was associated with imbalanced VD and PTH.

Background

In December 2019, clusters of acute pneumonia cases of unclear etiology were identified in Wuhan City, the capital of Hubei province in China[1−3]. The pathogen has been reported as a novel coronavirus that was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has declared that coronavirus disease 2019 (COVID-19) was a public health emergency of international concern[4]. Now the COVID-19 is spreading rapidly around the world, especially in South Korea, Italy, Iran and Japan[4]. As of March 02, a total of 80151 cases (2943 deaths) were confirmed in China, including 49426 cases (2251 deaths) in Wuhan city[5].

The National Health Commission of China has issued a series of diagnosis and treatment recommendations and suggested classifying the disease into four grades: mild, moderate, severe and critical[5]. Recent studies have reported the clinical characteristics and prognosis of COVID-19 with varied severity[1, 2, 6–8]. The underlying mechanisms of the novel coronavirus leading to disease aggravation and organs dysfunction remain to be further explored. Due to the high mortality and the lack of effective treatments in critical patients[7, 9], early identification and prediction of these patients is crucial. What are the risk factors for severe illness or death?[10] How can we identify groups most likely to have poor outcomes so that we can focus prevention and treatment efforts?[10] The studies are needed. Huang et al[8] reported that patients admitted into intensive care unit (ICU) had more severe clinical symptoms and more abnormal serum parameters. However, few literatures were published to confirm an early and sensitive biomarker to estimate the disease severity and prognosis of COVID-19. During our clinical work against the epidemic of COVID-19 in Wuhan, we observed a high incidence of hypocalcemia in critically ill patients. Therefore, we hypothesized that serum calcium levels were associated with the disease severity and prognosis of patients with COVID-19. This study was performed to test this hypothesis and explore the causes of hypocalcemia.

Methods

Patients

From February 10 to February 28 2020, adult patients (age ≥ 18 years) with confirmed COVID-19 admitted to our specialized isolation units, Tongji hospital of Huazhong University of Science and Technology in Wuhan were enrolled in this clinical retrospective study. Patients with chronic organ dysfunction (e.g., hepatic or renal dysfunction), terminal cancer, immunodeficiency, and patients with a history of long-term use of hormones were excluded. The written informed consent was waived by our institutional review board because this was a retrospective study that assessed de-identified data and included no potential risk to patients. The diagnosis of COVID-19 was according to WHO interim guidance and recommendations of National Health Commission of China[4, 5], and identified by RNA detection of the SARS-CoV-2 in clinical laboratory of Tongji hospital. The clinical outcomes (e.g., mortality, organ injury, discharges) were monitored up to March 06, 2020..

Definitions

A identified case of COVID-19 was defined as a positive finding on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens[4, 5, 7]. Only laboratory-confirmed cases were enrolled in the analysis. The clinical classifications of COVID-19 were in accordance with the Chinese recommendations[5]: Mild, minor clinical symptoms (e.g., fever, cough) without imaging manifestations; Moderate, fever, or respiratory tract infection symptoms with imaging indicating pneumonia; Severe, meet any of the following, I, respiratory distress, respiratory rate ≥ 30 breaths/min; II, pulse oxygen saturation (SpO2) ≤ 93% at rest; III, arterial partial pressure of oxygen

(PaO2)/ fraction of inspired oxygen (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa); Critical, meet any of the following, I, respiratory failure with mechanical ventilation (MV); II, shock; III, multiple organs failure requiring ICU treatment. Hypocalcemia was defined as serum calcium level less than 2.2 mmol/L. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, septic shock was defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality[11]. The diagnostic criteria of acute respiratory distress syndrome (ARDS) were in accordance with the Berlin definitions[12]. The definitions of acute kidney injury (AKI) were based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[13]. Cardiac injury was defined if serum levels of cardiac biomarkers (e.g., troponin I) were above than twice of the reference upper limit or new abnormalities were found in electrocardiography and echocardiography[2]. Liver injury was defined if serum levels of hepatic biomarkers (e.g., alanine aminotransferase) were above than twice of the reference upper limit or disproportionate elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels compared with alkaline phosphatase levels[14]. Multiple organ dysfunction syndrome (MODS) was defined as the combined dysfunction of two or more organs.

Data Collection

The baseline clinical characteristics, including age, sex, days from onset to admission, initial symptoms or signs, and clinical classifications were collected from electronic medical records, and all laboratory tests were performed according to the clinical needs of patients. The levels of serum calcium, C-reactive protein (CRP), ALT, albumin, creatinine, troponin I (TNI), plasma D-dimer, and white blood cells (WBC) count, lymphocyte count, the worst SpO2 within 24 hours of admission were recorded. The hormone levels associated with blood calcium (e.g., parathyroid hormone, 25-hydroxy-vitamin D) were also registered. All the blood parameters were detected by clinical laboratory of Tongji hospital. Moreover, The numbers of patients with ARDS, AKI, cardiac injury, liver injury, septic shock, MODS, and patients receiving noninvasive ventilation (NIV) /high-flow nasal cannula (HFNC) /MV, continuous renal replacement therapy (CRRT) were also recorded. The primary endpoints were the development of septic shock, MODS, and 28-day mortality. The secondary endpoints were the other disease severity parameters (e.g., organ injury or not).

Statistical analysis

The Kolmogorov-Smirnov test was first performed to test the normal distribution of the data. Normally distributed data were expressed as the means ± standard deviation and were compared by t tests. Abnormally distributed data were expressed as the medians (interquartile ranges, IQR) and were compared by the Mann-Whitney U test or the Kruskal-Wallis test. Categorical variables were presented as absolute numbers or percentages and were analyzed using the χ^2 test or Fisher's exact test. To take into account the repeated nature of the variables, analysis of variance (ANOVA) for repeated measurements of the general linear model was implemented. Receiver operating characteristic (ROC) curves were used to

evaluate the associations between serum calcium and septic shock, MODS, and 28-day mortality. IBM Statistical Package for the Social Sciences (SPSS, version 22.0, NY, USA) software was used for statistical analysis, and P < 0.05 was considered statistically significant. SPSS scatterplots and a correlation analysis were performed to evaluate the relevance between serum calcium and blood biomarkers. The statistical methods of this study were reviewed by Qiao Liu, a biostatistician from the Center for Disease Control and Prevention of Jiangsu Province in China.

Results

A total of 241 patients with confirmed COVID-19 were enrolled in this clinical retrospective study. The median age was 65 (IQR, 55–72) years, and 129 (53.5%) were women. Of these patients, 192 was classified as severe (167/214, 69.3%) or critical (25/214, 10.5%). Fever (108/214, 44.8%) and cough (65/214, 27.0%) were the main initial symptoms. One hundred and eighty (180/214, 74.7%) patients had hypocalcemia on admission. The detailed clinical data of the patients were presented in Table 1. As of March 06, 94 patients were discharged from hospital, median hospital stay was 15 (IQR, 11–18) days. MODS developed in 17 (7.1%) patients, septic shock in 6 (2.5%) patients. Ten (10/241, 4.1%) patients died within 28 days of admission, all of which were critical. In other words, the 28-day mortality of critical patients was 40.0% (10/25).

Table 1
Demographic data and clinical parameters

Variables	Values
Age (years)	65 (55−72)
Sex (Male: Female)	112:129
Days from onset to admission	13 (10−16)
Initial symptoms or signs (n, %)	
Fever	108 (44.8%)
Cough	65 (27.0%)
Chest tightness or pain	22 (9.1%)
Fatigue	10 (4.1%)
Dyspnea	9 (3.7%)
Diarrhea	7 (2.9%)
Pharyngalgia	5 (2.1%)
Myalgia	5 (2.1%)
Nausea or vomiting	4 (1.7%)
Abdominal pain	3 (1.2%)
Other	3 (1.2%)
Classifications	
Mild	0 (0%)
Moderate	49 (20.3%)
Severe	167 (69.3%)
Critical	25 (10.4%)
Blood parameters	
Calcium (mmol/L)	2.12 (2.04−2.20)
CRP (mg/L)	6.30 (1.70-34.85)
WBC (10^9/L)	5.48 (4.55−7.15)

CRP, C-reactive protein; WBC, white blood cells; ALT, alanine aminotransferase; TNI, troponin I; SpO2, pulse oxygen saturation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; MV, mechanical ventilation; CRRT, continuous renal replacement therapy.

Variables	Values
Lymphocyte (10^9/L)	1.26 (0.93–1.63)
ALT (U/L)	22.0 (14.0–36.0)
Albumin (g/L)	35.6 (31.6–38.8)
Creatinine (umol/L)	66.0 (56.0–80.0)
TNI (pg/mL)	3.80 (1.95–7.45)
D-dimer (ug/mL)	0.73 (0.34–1.42)
Worst SpO2 (%)	97.0 (96.0–98.0)
Organs injury (n, %)	
ARDS	19 (7.9%)
Liver injury	16 (6.6%)
AKI	14 (5.8%)
Cardiac injury	12 (5.0%)
Septic shock (n, %)	6 (2.5%)
Need for NIV /HFNC (n, %)	7 (2.9%)
Need for MV (n, %)	12 (5.0%)
Need for CRRT (n, %)	7 (2.9%)
Discharged (n, %)	94 (39.0%)
Death (n, %)	10 (4.1%)

CRP, C-reactive protein; WBC, white blood cells; ALT, alanine aminotransferase; TNI, troponin I; SpO2, pulse oxygen saturation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; MV, mechanical ventilation; CRRT, continuous renal replacement therapy.

Serum Calcium And Clinical Variables

The median serum calcium levels were 2.12 (IQR, 2.04–2.20) mmol/L on admission. We divided patients into three groups based on the serum calcium values: ≤2.0 mmol/L (defined as group A, n = 43), 2.0-2.2 mmol/L (defined as group B, n = 137), and > 2.2 mmol/L (defined as group C, n = 61). As shown in Table 2, significant differences in the clinical variables were found among the three groups except for serum creatinine, same results were found between group A and B (P < 0.05). There were also differences in these variables except for WBC count (P = 0.07) and serum creatinine (P = 0.244) between group A and

C, whereas except for WBC conut (P = 0.60), ALT (P = 0.839), the worst SpO2 (P = 0.328), and serum creatinine (P = 0.635) between group B and C. These results indicated that patients with lower serum calcium levels had worse clinical variables.

Table 2
Serum calcium and clinical parameters

	Group A (n = 43)	Group B (n = 137)	Group C (n = 61)	P value
Calcium (mmol/L)	1.96 (1.91-2.00)	2.11 (2.06−2.13)	2.22 (2.21−2.26)	< 0.001
CRP (mg/L)	47.4 (20.5-105.7)	6.3 (1.9−25.8)	2.0 (0.8−6.2)	< 0.001
WBC (10^9/L)	6.58 (4.57−9.01)	5.36 (4.38−6.79)	5.29 (4.67−6.96)	0.042
Lymphocyte (10^9/L)	0.75 (0.50−1.19)	1.27 (1.01−1.63)	1.53 (1.17−1.75)	< 0.001
ALT (U/L)	32.0 (18.0−51.0)	20.0 (14.0-34.5)	20.0 (13.0-35.5)	0.027
Albumin (g/L)	30.6 (28.2−32.6)	35.6 (31.7−38.4)	40.0 (36.1−43.2)	< 0.001
Creatinine (umol/L)	66.0 (61.0−79.0)	67.0 (55.5−80.0)	64.0 (57.0−80.0)	0.565
TNI (pg/mL)	8.80 (3.90−16.70)	3.40 (1.95−6.20)	2.50 (1.90−4.55)	< 0.001
D-dimer (ug/mL)	1.30 (0.74−8.29)	0.68 (0.34−1.37)	0.43 (0.27−0.80)	< 0.001
Worst SpO2 (%)	96.0 (90.0−97.0)	97.0 (96.0−98.0)	97.0 (96.0−98.0)	< 0.001

Group A, the serum calcium values: ≤2.0 mmol/L; Group B, the serum calcium values: 2.0-2.2 mmol/L; Group C, the serum calcium values: >2.2 mmol/L; CRP, C-reactive protein; WBC, white blood cells; ALT, alanine aminotransferase; TNI, troponin I; SpO2, pulse oxygen saturation.

Of the 241 patients, 26 were tested for hormone levels of parathyroid hormone (PTH) and 25-hydroxy-vitamin D (VD) according to the clinical needs. The median serum calcium levels of the 26 patiens were 2.13 (IQR, 2.03−2.16) mmol/L. The median PTH levels were 55.27 (IQR, 42.73−73.15) pg/mL, median VD levels were 10.20 (IQR, 8.20-12.65) ng/mL. All of these patients had low levels of VD (VD deficiency).

SPSS scatterplots and correlation analyses of serum calcium and these blood biomarkers were shown in Figs. 1 and 2. The serum calcium levels were significantly positive correlated with lymphocyte count (Fig. 1A, P < 0.001), albumin (Fig. 1B, P < 0.001), VD (Fig. 1C, P = 0.004), and worst SpO2 (Fig. 1D, P < 0.001) levels, whereas significantly negative correlated with CRP (Fig. 2A, P < 0.001), D-dimer (Fig. 2B, P < 0.001) and PTH (Fig. 2C, P = 0.048) levels. These results indicated that hypocalcemia may be associated with imbalanced VD and PTH in the acute phase of COVID-19.

Serum Calcium And Clinical Severity

ARDS developed in 19 of 241 (7.9%) patients, liver injury developed in 16 (6.6%), AKI developed in 14 (5.8%), and cardiac injury developed in 12 (5.0%) during the research period. Twelve patients received MV, and 7 patients received CRRT. As shown in Table 3, significant differences in the clinical severity and outcome variables were found among the above-mentioned three groups (A, B, and C) (P < 0.001). Same results were also found between group A and C (P < 0.001). There were also differences in these variables except for liver injury incidence (P = 0.201). No differences in these variables were found between group B and C (P > 0.05). These results indicated that patients with serum calcium values ≤ 2.0 mmol/L had higher 28-day mortality, higher incidence of organ injury. Moreover, the serum calcium values were significantly lower in dead patients and in patients with MODS, septic shock, organs injury, requiring MV or CRRT (P < 0.001) (shown in Table 4).

Table 3
Serum calcium and clinical variables of severity and outcomes

	Group A (n = 43)	Group B (n = 137)	Group C (n = 61)	P value
Death	10	0	0	< 0.001
MODS	14	3	0	< 0.001
Septic shock	6	0	0	< 0.001
ARDS	15	3	1	< 0.001
Liver injury	6	9	1	< 0.001
AKI	8	5	1	< 0.001
Cardiac injury	7	5	0	< 0.001
Need for MV	12	0	0	< 0.001
Need for CRRT	7	0	0	< 0.001

Group A, the serum calcium values: ≤2.0 mmol/L; Group B, the serum calcium values: 2.0-2.2 mmol/L; Group C, the serum calcium values: >2.2 mmol/L; MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; MV, mechanical ventilation; CRRT, continuous renal replacement therapy.

Table 4

Values of serum calcium in relation to the presence or absence of clinical variables of severity and outcomes

Clinical variables	Presence		Absence		P value
	serum calcium	n	serum calcium	n	
Death	1.96 (1.90-2.00)	10	2.12(2.05−2.20)	231	< 0.001
MODS	1.95 (1.88-2.00)	17	2.13 (2.06−2.20)	224	< 0.001
Septic shock	1.98(1.92-2.00)	6	2.12(2.05−2.20)	235	< 0.001
ARDS	1.95 (1.90-2.00)	19	2.13(2.06−2.20)	222	< 0.001
Liver injury	2.04 (1.96−2.06)	16	2.12(2.05−2.20)	225	< 0.001
AKI	1.97(1.87−2.07)	14	2.12(2.05−2.20)	227	< 0.001
Cardiac injury	2.00 (1.90−2.07)	12	2.12(2.05−2.20)	229	< 0.001
Need for MV	1.94(1.89-2.00)	12	2.12(2.05−2.20)	229	< 0.001
Need for CRRT	1.91(1.84−1.94)	7	2.12(2.05−2.20)	234	< 0.001

MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; MV, mechanical ventilation; CRRT, continuous renal replacement therapy.

The ROC curves were also performed to assess the associations between serum calcium and MODS, septic shock, and 28-day mortality. As shown in Fig. 3, the area under curves (AUCs) of MODS (Fig. 3A), septic shock (Fig. 3B), and 28-day mortality (Fig. 3C) were 0.923 (P < 0.001), 0.905 (P = 0.001), and 0.929 (P < 0.001), respectively. Optimal cut-off points of serum calcium values were derived from the ROC curves. The optimal cut-off point for MODS was 2.035 mmol/L, the sensitivity was 88.2%, and the specificity was 82.6%. The optimal cut-off point for septic shock was 2.01 mmol/L, the sensitivity was 100.0%, and the specificity was 84.3%. The optimal cut-off point for 28-day mortality was 2.01 mmol/L, the sensitivity was 100.0%, and the specificity was 85.7%.

Discussion

This clinical retrospective study investigated the correlations between serum calcium and clinical severity and outcomes in patients with COVID-19. The incidence of hypocalcemia was 74.7%. We found that patients with lower serum calcium levels (especially ≤ 2.0 mmol/L) had worse clinical variables, higher incidence of MODS, septic shock and higher 28-day mortality. The hypocalcemia may be associated with imbalanced VD and PTH in the acute phase of COVID-19. The overall mortality was 4.1% (10/241), whereas the mortality of critical patients was up to 40.0% (10/25).

The WHO declared that COVID-19 was a public health emergency of international concern, because this unclear acute infectious disease is spreading rapidly around the world [4]. There are more than 100000 patients was diagnosed as COVID-19 worldwide, and nearly 3500 of them died[4]. Although the National Health Commission of China and WHO has issued a series of diagnosis and treatment recommendations, the mortality of critical patients was still extremely high. The underlying mechanisms of the novel coronavirus causing organs dysfunction were unknown yet. It is crucial to identify the risk factors for severe illness or death[10]. However, few reports were published to establish an early and sensitive biomarker to predict the disease severity and prognosis of COVID-19. In this study, we found that serum calcium levels were associated with the disease severity and prognosis of patients with COVID-19.

Hypocalcemia is common in critically ill patients. The causes of hypocalcemia include oversecretion of PTH, VD deficiency, decreased diet, hypoproteinemia, hypomagnesemia drug interactions, and so on[15]. Moreover, hypocalcemia was considered to be associated with organ dysfunction and poor outcomes in critically ill patients[15]. The findings of this study were consistent with previous reports. However, this was the first study to investigate the correlations between serum calcium and clinical outcomes in patients with COVID-19. We found that patients with serum calcium values ≤ 2.0 mmol/L had higher 28-day mortality, higher incidence of organ injury. These results suggested that redressing of hypocalcemia could be an important strategy to improve the prognosis of patients with COVID-19, especially for patients with serum calcemia less than 2 mmol/L. In addition, our study also revealed that hypocalcemia was associated with hypoproteinemia, imbalanced VD and PTH in the acute phase of COVID-19. The hypoproteinemia and deficiency of VD were also common and correlated with increased mortality in critically ill patients[16, 17]. Therefore, improvement of hypoproteinemia and imbalanced hormone levels may also be useful in the treatments of COVID-19.

Increased CRP, ALT, TNI, D-dimer, and lymphocytopenia were present in most of critical COVID-19 patients[2, 7, 8]. Our results also showed that patients with lower serum calcium values had higher levels of CRP, ALT, TNI, D-dimer and lower lymphocyte counts. The serum calcium values were significantly correlated with lymphocyte count, CRP and D-dimer levels. Moreover, CRP and D-dimer were also the indicators to predict the prognosis of critically ill patients[17]. The findings of this study were consistent with the previous reports and also confirmed that serum calcium levels were associated with the disease severity and prognosis of patients with COVID-19. Lung is the main organ involved in this disease. In this study, the median worst SpO2 were 97.0% (IQR, 96.0%-98.0%; range, 80%-99%), and the SpO2 values were significantly positive correlated with serum calcium levels. Patients with serum calcium values ≤ 2.0 mmol/L had higher ARDS incidence, while patients with ARDS also had lower serum calcium values. These phenomena indicated that hypocalcemia might play a potential role in the development of ARDS. Early diagnosis and treatment of hypocalcemia may alleviate organ injury in the acute phase of COVID-19.

Some limitations of the study should be discussed. Because of our single-center retrospective design and small sample size, the results might be inconclusive, and the accuracy should be confirmed by large-scale clinical prospective studies. Moreover, because the study was not based on pathophysiological models,

the results were hypothesis generating, the exact mechanisms of hypocalcemia and VD deficiency should be tested by more basic experiments. In addition, the values of serum calcium were total calcium rather than ionized calcium in this study, which may not reflect precisely the extent of decreased calcium.

Conclusions

This retrospective clinical study found that the incidence of hypocalcemia and VD deficiency was very high in patients with COVID-19. Hypocalcemia may be associated with imbalanced VD and PTH levels. Patients with lower serum calcium levels (especially ≤ 2.0 mmol/L) had worse clinical variables, higher incidence of MODS, septic shock and higher 28-day mortality. The overall mortality of COVID-19 was 4.1%, whereas the mortality of critical patients was up to 40.0%.

Declarations

Abbreviations

COVID-19: coronavirus disease 2019; PTH: parathyroid hormone; VD : 25-hydroxy-vitamin D; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; ICU: intensive care unit; RT-PCR: real-time reverse-transcriptase–polymerase-chain-reaction; PaO2: arterial partial pressure of oxygen; FiO2: fraction of inspired oxygen; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; KDIGO: Kidney Disease: Improving Global Outcomes; ALT: alanine aminotransferase; AST: aspartate aminotransferase; MODS: multiple organ dysfunction syndrome; CRP: C-reactive protein; TNI: troponin I; WBC: white blood cell; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; CRRT: continuous renal replacement therapy; IQR: interquartile ranges; ANOVA: analysis of variance; ROC: receiver operating characteristic; SPSS: statistical package for the social sciences.

Acknowledgements

The authors thank Qiao Liu for her assistance in the statistical analysis of this study. The authors also thank Li H, Zou J, Dong K, and Jin CC of Tongji hospital for their contributions to this study. In addition, Sun JK and his family especially thank Sun XP for her meticulous care and support during the past ten years.

Authors' contributions

Sun JK, Zhang WH, Shi QK, Yuan ST, Gu W, and Qi JW designed the research; Sun JK, Zhang WH, Zou L, Liu Y, Li JJ, Kan XH, Dai L performed the research; Sun JK, Zhang WH, Yu WK, and Xu HY analyzed the data; Sun JK and Zhang WH wrote the paper.

Fundings

YKK18108).

Availability of data and materials

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

Ethics approval and consent to participate

The study was reviewed and approved by the institutional review board of Nanjing First Hospital and Tongji Hospital, whereas written informed consent was waived because this was a retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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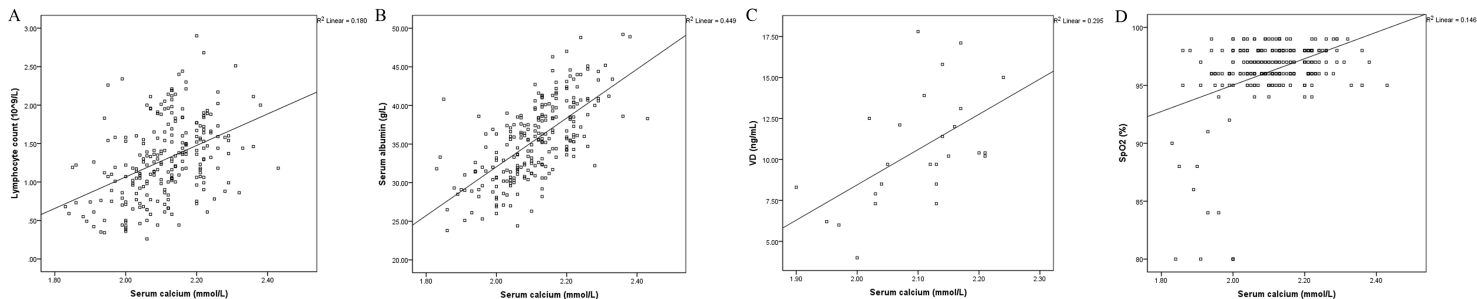
Figures

Figure 1

The serum calcium levels were positively correlated with lymphocyte count (Fig 1A, P <0.001), albumin (Fig 1B, P <0.001), 25-hydroxy-vitamin D (VD) (Fig 1C, P =0.004), and worst SpO2 (Fig 1D, P< 0.001) levels.
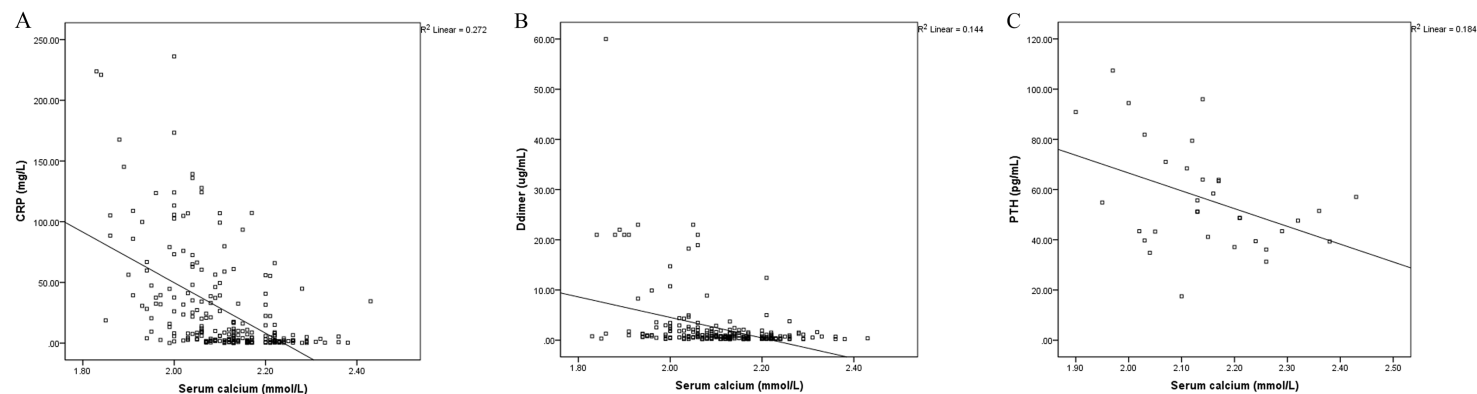

Figure 2

The serum calcium levels were negative correlated with C-reactive protein (CRP) (Fig 2A, P< 0.001), D-dimer (Fig 2B, P< 0.001) and parathyroid hormone (PTH) (Fig 2C, P =0.048) levels.
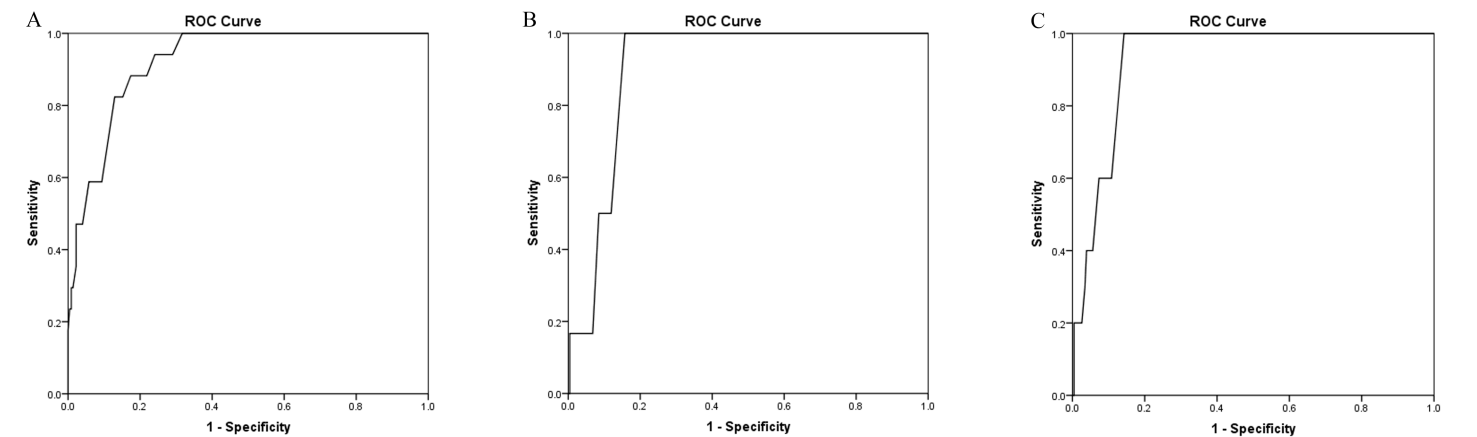

Figure 3

The areas under the receiver operating characteristic curves of multiple organ dysfunction syndrome (Fig 3A), septic shock (Fig 3B), and 28-day mortality (Fig 3C) were 0.923 (P <0.001), 0.905 (P =0.001), and 0.929 (P <0.001), respectively.