THE CORRELATION BETWEEN THE HYPOALBUMINAEMIA AND HYPOCALCAEMIA IN SEPSIS PATIENTS: A RETROSPECTIVE STUDY FROM MIMIC-III

Weijia Li, Lei Huang, Hua Luo, Weixing Zhang, Wencheng He*
Department of Intensive Care Unit, Peking University Shenzhen Hospital, No,1120, Lianhua Road, Futian District, Shenzhen, 518000, China

ABSTRACT

Objective*: Hypoalbuminemia and hypocalcaemia are two common abnormalities in sepsis, little is known about their possible correlation during the sepsis process. We investigated the correlation between hypoalbuminemia and hypocalcaemia and their combinatorial effects on the prognosis in sepsis.*

Methods*: Eligible septic patients were extracted from the MIMIC-III database. Cox-regression analysis was performed to examine the potential risk of hypoalbuminemia combined with hypocalcaemia on the mortality in the septic patients. The possible correlation between the serum albumin and calcium was examined by Pearson correlation analysis, and the various effects of different doses of albumin supplementation on the serum calcium level and prognosis were also examined.*

Result*: There were more than 60% of septic patients who had hypoalbuminemia hypocalcaemia during the ICU admission, In the marked hypoalbuminemia groups, patients with normal calcium level displayed the highest risk on mortality (OR: 7.714, 95% CI 3.292-18.075; p<0.001), while patients with marked hypocalcaemia have a relatively lowest risk on mortality (OR: 7.714, 95% CI 3.292-18.075; p<0.001). Cross-sectional analysis further showed that either total calcium (r=-0.950, p=0.004) or iron calcium (r=-0.904, p= 0.013) was found to be negatively correlated with the albumin during the ICU stay, and non-survivors had lower albumin and total calcium level in comparison with the survivors. The higher dose of albumin supplementation might down regulate the total calcium level and displayed lower mortality.*

Conclusion*: Hypoalbuminemia and hypocalcaemia exhibited negative correlation in septic patients during their ICU stay. Hypocalcaemia might be protective in the septic patients who with marked hypoalbuminemia.*

Keywords: *Sepsis, Hypoalbuminaemia, Hypocalcemia, Correlation, Mortality, Retrospective study.*

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Background

The physiological importance of albumin and calcium has been found to be immense. The serum albumin accounts for 55% of the total protein and is essential for maintaining the osmotic pressure between the blood vessels and the body tissues, its level can serve as a potential marker for the nutritional deficiency. Whereas calcium as a ubiquitous mineral element can act as an important intracellular secondary messenger as well as a coenzyme in eukaryotic cells, and it can modulate cellular life from its origin at the stage of fertilization to its ultimate end. Approximately 40% of calcium is bound to different proteins, mostly albumin, and 45% circulates as active ironed calcium, whereas the remainder is bound to the various organic and inorganic anions[1]. Malnutrition in these two elements is common in the ICU setting, particularly in the septic patients. Hypoalbuminemia has been reported to be a commonly occurring independent condition associated with outcome in sepsis[2-4], while the previous studies about the role of hypocalcemia in critically ill patients have yielded conflicting results. Patients with severe hypocalcemia can lead to the several life-threatening complications

and therefore might lead to a poor outcome[5, 6]. However, some previous studies have suggested that mild hypocalcaemia in the septic patients can be potentially protective and attempted correction can lead to harmful effects[7, 8].

Though the pathophysiology of hypoalbuminemia[9-11] and hypocalcemia[7, 12, 13] in sepsis have been well studied previously, little is known about their possible correlation during the sepsis process, and the significance of the various severe combination of hypoalbuminemia and hypoglycemia in the prognosis has yet to be clarified. In this study, the septic patient's data was extracted from the Medical Information Mart for Intensive Care III (MIMIC-III) database, and the potential correlation between the hypoalbuminemia and hypocalcaemia in patients during early ICU stay, and the mortality risk when the two conditions were combined were analyzed. The rationale of this study was to shed light on the pathophysiology of hypoalbuminaemia combined with hypocalcaemia in sepsis, which might benefit early identification of high mortality risk according to the serum albumin and calcium status in sepsis and thus facilitate better clinical decision-making.

Database and Cohort Selection

We employed the MIMIC-III database in this study. The MIMIC-III database contains 58,976 de-identified ICU patients who were admitted to Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2001 to 2012. Our access to the database was approved after completion of the CITI program course named "Human Research-Data or Specimens Only Research" and passing the Protecting Human Research Participants exam (NO. 31532119). The institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center approved this study, and informed consent was waived due to the purely observational nature of the study. The Clinical Research Review Committee of Peking University Shenzhen Hospital also approved this study. The extraction of septic patients was closely adhered to the Sepsis-3 definitione (total SOFA score of 2 points or more and was infectious), and the exclusion criteria have been described in Figure 1. To compare the clinical characteristics among the patients with albumin or calcium or both of them replacement, they were stratified into the four different groups as follows: patients without albumin and calcium supplement, with only calcium supplement, with only calcium supplement, and with both the calcium and albumin supplement. We also extracted clinical data, including patient demographics and laboratory test results. Structured Query Language (SQL) with PostgreSQL (version 9.6) was used to extract the data from MIMIC-III.

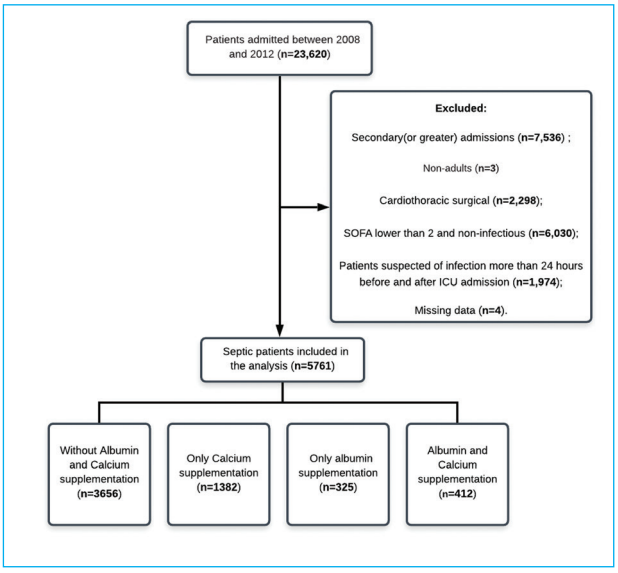

Figure 1: Illustration of exclusion and inclusion criteria utilized to select the final cohort of 5761 patients.

Statistical Analysis

Kolmogorov-Smirnov test was used for the normal distribution analysis. The continuous variables with a normal distribution were expressed as the mean ± standard deviation (SD) and compared using Student's T test; otherwise, data was expressed as the median with quartiles and was compared using the Mann-Whitney U test. The categorical variables have been expressed as percentages and were compared using the Chi-square test or Fisher's exact test as appropriate.

The blood albumin and total calcium stage was defined accordance with the clinical regulations of our department, which showed as follows: mild hypoalbuminemia (2.5-3.5 mg/dL); marked hypoalbuminemia (<2.5 mg/dL); mild hypocalcaemia (8.0-8.5 mg/dL); marked hypocalcaemia <8.0 mg/dL. To avoid the albumin or calcium supplementation effect on the blood albumin and calcium level, only the subgroup of patients without albumin and calcium supplementation during the ICU stay were included to investigate the potential association between the albumin and serum calcium levels by using Pearson correlation analysis. To further determine whether the difference level of serum albumin and calcium have an effect on hospital mortality, cases were further classified into the various groups based on

the blood albumin and total calcium level measured at the time of admission.

Group distribution was carried out as described: 1. Non-hypoalbuminemia plus non-hypocalcaemia (patients with a albumin ≥ 3.4 mg/dl and total calcium> 8.5 mg/dL), 2. non-hypoalbuminemia plus mild hypocalcaemia (patients with a albumin > 3.4 mg/dl as well as the total calcium between 8.0 and 8.5 mg/dL), 3. non-hypoalbuminemia plus marked hypocalcaemia (patients with a albumin > 3.4 mg/dl and the total calcium less than 8.0 mg/dL), 4. mild hypoalbuminemia plus non-hypocalcaemia (patients with a albumin between 2.5 and 3.4 mg/dl as well as the total calcium more than 8.5 mg/dL), 5. mild hypoalbuminemia plus mild hypocalcaemia (patients with albumin level between 2.5 and 3.4 mg/dl and the total calcium between 8.0 and 8.5 mg/dL), 6. mild hypoalbuminemia and marked hypocalcaemia (patients with albumin between 2.5 and 3.4 mg/dl and blood calcium less than 8.0 mg/dL), and 7. marked hypoalbuminemia as well as marked hypocalcaemia (patients with a blood albumin less than 2.5 mg/dl and blood calcium less than 8.0 mg/dL).

The risk of the mortality of albumin levels in the patients with hypocalcaemia was analyzed at the time of admission. The patients with various subgroups were compared with the non-hypoalbuminaemia and non-hypocalcaemia patients by using COX regression models, and the data was expressed as the Hazard ratio with pertinent 95% confidence interval (CI).

The statistical analyses were performed using the software IBM SPSS statistic (vision 25). Two-tailed P value <0.05 was considered to be statistically significant.

Results

The positive and negative effect of hypocalcaemia on the prognosis in septic patients depend on the severity of hypocalcaemia and hypoalbuminaemia

5,761 different septic patients were included for the analysis, and of those, 3656 (63.46%) without calcium as well as albumin supplement, 1382 (23.99%) with calcium supplement, 325 (5.64%) patients with albumin supplement, and 412 (7.15%) patients with both calcium and albumin supplement. The clinical characteristics of these patients have been shown in Table 1. In the case of those patients, who had their albumin and total calcium measured on the first day after admission, 60.09% had hypoalbuminemia hypocalcaemia, 14.45% had hypocalcaemia, 11.31% had hypoalbuminemia, and 13.95% were found to have normal serum albumin and calcium level (Figure 2).

	Supplementation				
	Without calcium can albumin supplement (n=3656, 63.46%)	Only Calcium (n=1382, 23.99%)	Only albumin (n=325, 5.64%)	Calcium and albumin (n=412, 7.15%)	P
Age (years; median, Q_1-Q_3)	68.03(54.79-81.01)	65.14(52.02-78.25)	65.99(56.65-76.83)	64.29(52.03-77.05)	0.267
Male (male; n, %)	2014(55%)	785(56.80%)	186(57.23%)	234(56.55%)	0.628
race_white (n,%)	2674(73.14%)	968(70.04%)	243(74.77%)	307(74.51%)	0.086
race_black (n,%)	353(9.67%)	119(8.61%)	14(3.4%)	17(5.23%)	<0.001
race_hispanic (n,%)	121(3.31%)	44(3.18%)	10(3.08%)	13(3.16%)	0.992
race_other (n,%)	508(13.89%)	251(18.16%)	55(16.92%)	78(18.93%)	<0.001
Albumin level on first ICU admission	3.1(2.7-3.5)	2.93(2.5-3.3)	2.60(2.15-3.15)	2.67(2.3-3.2)	<0.001
Iron Calcium on first ICU admission	1.125(1.08-1.18)	1.08(1.03-1.13)	1.13(1.09-1.18)	1.09(1.03-1.13)	<0.001
Total Calcium on first ICU admission	8.2(7.75-8.7)	7.80(7.35-8.35)	8.05(7.6-8.55)	7.9(7.35-8.4)	<0.001
Severity					
SOFA (mean±SD)	4(3-6)	5(3-8)	6(4-9)	7(4.25-10)	<0.001
Sirs (mean±SD)	4(2-6)	5(3-7)	6(4-8)	6(4-8)	<0.001
Lods (mean±SD)	2(1-2)	3(3-4)	3(2-4)	3(3-4)	<0.001
Qsofa (mean±SD)	2(1-2)	2(2-2)	2(2-2)	2(2-2)	<0.001
Sepsis shock (n,%)	300(8.20%)	279(20.19%)	46(14.15%)	113(27.43%)	<0.001
ICU los (days; median, Q1–Q3)	1.965(1.21-3.51)	3.93(2.05-7.97)	4.02(2.22-8.02)	8.56(4.19-16.59)	<0.001
Hospital los (days; median, Q1–Q3)	6.482(3.9-10.02)	8.99(5.24-15.29)	11.64(7.04-17.75)	16.52(9.95-26.52)	<0.001
Hospital death (days; median, Q1–Q3)	378(10.31)	277(20.07%)	54(16.62%)	121(29.37%)	<0.001

Table 1: The clinical characteristics of septic patients with or without albumin and calcium supplementation.
SOFA, Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome, LODS, Logistic Organ Dysfunction System; ICU LOS, intensive care unit length of stay; Hospital LOS, Hospital length of stay.

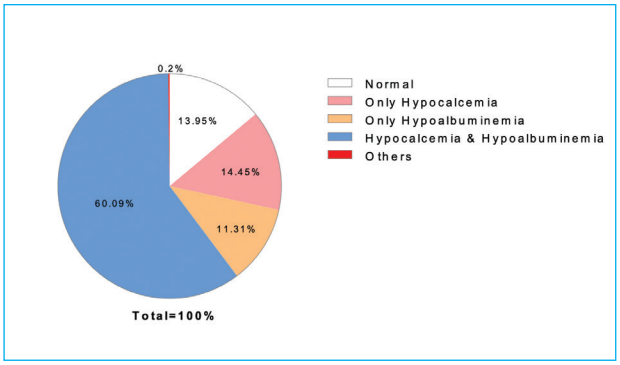

Figure 2: The percentage of only hypocalcaemia, only hypoalbuminemia or patients with hypocalcaemia and hypoalbuminemia combination at the time of the first ICU admission.

In patients, who had calcium and albumin supplement during the ICU stay were more severe compare with others, as highest SOFA score and hospital mortality (29.37%), and longest ICU and hospital stay (8.56 (4.19-16.59) days, 16.52 (9.95-26.52), respectively) were observed, while patients without calcium and albumin supplement had lowest mortality (10.31%) and shortest ICU stay (1.97 (1.21-3.51)) and hospital stay (6.48 (3.90-10.02)), respectively. Moreover, the albumin supplement group was found to be more severely affected as compared to the calcium supplement group, as the SOFA score, the occurrence of septic shock, length

of ICU and hospital stay were significantly higher in the albumin supplement group, thereby implying that serum albumin disturbance can pose a higher risk of poor prognosis as compared to the calcium disorder.

The patients were also stratified into the various categories according to severity of hypoalbuminaemia and hypocalcaemia, respectively, and the clinical characteristics for each group have been shown in Table 2.

	Total	non-hypoalbuminemia + non-hypocalcaemia	non-hypoalbuminemia + mild hypocalcaemia	non-hypoalbuminemia + marked hypocalcaemia	mild hypoalbuminemia + non-hypocalcaemia	mild hypoalbuminemia + mild hypocalcaemia	mild hypoalbuminemia + marked hypocalcaemia	marked hypoalbuminemia + non-hypocalcaemia	marked hypoalbuminemia + mild hypocalcaemia	marked hypoalbuminemia + marked hypocalcaemia	p
Case: number	1162((100%)	215(18.5%)	123(10.59%)	68(5.85%)	126(10.84%)	169(14.54%)	275(23.67%)	9(0.77%)	23(1.98%)	154(13.25%)	
Age (years; median, Q_1-Q_3)	66.73(53.18-79.18)	69.1(54.64-81.07)	66.13(50.7-79.00)	59.45(45.88-70.28)	63.82(53.29-77.07)	66.65(53.86-79.45)	68.52(52.03-80.72)	75.5(66.9-88.12)	74.65(60.34-83.43)	66.07(53.88-77.98)	0.002
Male (male; n, %)	640(55.08%)	116(53.95%)	79(64.23%)	39(57.35%)	63(50%)	90(53.25%)	144(52.36%)	7(77.78%)	12(52.17%)	90(58.44%)	0.307
SOFA (mean±SD)	5(3-7)	4(3-5)	4(3-6)	4(3-6)	5(3-7)	5(3.5-6)	5(4-7)	6(3.5-10)	6(4-8)	6(4-8)	<0.001
Sepsis shock (n, %)	128(11.02%)	2(0.93%)	5(4.07%)	8(11.76%)	2(1.59%)	15(8.88%)	52(18.91%)	0(0%)	3(13.04%)	41(26.62%)	<0.001
ICU los (days; median, Q_1-Q_3)	2.091(1.33-3.82)	1.983(1.21-3.77)	2.111(1.4-3.99)	1.819(1.23-3.34)	2.203(1.57-3.66)	2.089(1.28-3.78)	2.044(1.28-3.83)	1.1(0.75-3.82)	2.591(1.99-6.82)	2.242(1.59-4.04)	0.354
Hospital los (days; median, Q_1-Q_3)	6.638(3.97-11.24)	6.139(3.65-11.52)	6.757(4-8.86)	6.62(3.75-9.65)	7.777(4.7-13.21)	7.094(4.81-12.89)	6.148(3.85-9.48)	4.733(0.68-15.44)	9.248(4.69-16.98)	6.505(4-12.05)	0.041
Hospital mortarity (n, %)	159(13.68%)	24(11.16%)	7(5.69%)	10(14.71%)	19(15.08%)	18(10.65%)	35(12.73%)	7(77.78%)	8(34.78%)	31(20.13%)	<0.001

Table 2: The clinical characteristics of 1162 septic patients (without albumin and total calcium records censor) but with the different levels of serum albumin and total calcium combination.

SOFA, Sequential Organ Failure Assessment; ICU LOS, intensive care unit length of stay; Hospital LOS, Hospital length of stay.

		Serum Albumin level					
		Non-hypoalbuminemia		Mild hypoalbuminnia		Marked hypoalbuminnia	
		Hazard Ratio (95% Confidence Interval)	p	Hazard Ratio (95% Confidence Interval)	p	Hazard Ratio (95% Confidence Interval)	p
Blood calcium level	Non-hypocalcemia	Reference	/	1.199 (0.656-2.192)	0.555	7.714 (3.292-18.075)	<0.001
	Mild hypocalcaemia	0.504 (0.217-1.170)	0.111	0.903 (0.490-1.665)	0.774	2.656 (1.190-5.928)	0.017
	Marked hypocalcaemia	1.379 (0.658-2.887)	0.395	1.120 (0.662-1.898)	0.672	1.772 (1.101-2.936)	0.046

Table 3: Univariate Cox regression analyses of the septic patients with different severity of hypoalbuminemia and hypocalcaemia (total calcium).

We found that the sofa score was significantly increased in the cases with worse hypoalbuminaemia, whereas the occurrence of sepsis shock was increased significantly along with the cases with worse hypocalcaemia. The highest mortality rates (77.78%) were seen in patients with marked hypoalbuminaemia but normal calcium level, while the lowest mortality rate (5.69 %) was observed in patients with the normal albumin level but mild hypocalcemia, a lower mortality (10.65%) was also noticed in mild hypocalcaemia patients in mild hypoalbuminaemia groups, this distinct trend suggested that the marked hypocalcaemia changed from a hazard into the protective condition along with an increase severity of hypoalbuminaemia. The result of Cox regression analysis also showed that the highest mortality risk was seen in patients with marked hypoalbuminemia but not in those with the normal calcium level group (OR: 7.714, 95% CI: 3.292-18.075; p<0.001); however, the risk of mortality dropped significantly when a marked hypocalcaemia was present (OR: 1.772, 1.101-2.936; p=0.046) (Table 3).

Serum albumin negative correlated with the total calcium in septic patients during the ICU stay

To investigate the possible correlation between the hypocalcaemia and hypoalbuminaemia during sepsis process, we analyzed the dynamics of serum albumin, total calcium and iron calcium in the septic patients who were without calcium and albumin replacement for 6 days after ICU admission. We found that both albumin and calcium levels reduced under the normal range in the first day of ICU admission, the results of Pearson correlation analysis showed that there was a significant positive regressions of total (R^2=0.150, p<0.0001) and iron calcium (R^2=0.016, p=0.045) on albumin during the first ICU admission (Figure 3). However, either the total calcium (r=-0.950, p=0.004, Figure 4A) or iron calcium (r=-0.904, p= 0.013, Figure 4B) was negatively correlated with the albumin during the following day after the ICU admission. There was a tendency that albumin dropped gradually during the ICU stay, while the total calcium and iron calcium increased gradually as time passed by, and the non-survivors suffered greater albumin loss as compared to the survivor (Figure 5A). The total calcium in survivor was significantly higher than that in non-survivors but still under the normal level and up-regulated gradually as the time passed by (Figure 5B), while the iron calcium in survivor were much more steady as compared to those in the non-survivors and were maintained in a mild hypocalcaemia range (Figure 5 C), suggesting that higher level of the serum albumin and mild hypocalcaemia might benefit the prognosis of sepsis.

Higher dose of albumin might down regulate the total calcium level and benefit the prognosis of sepsis

There are two different types of albumin supplements (higher dose: 5% (25g/ 500 mL) and lower dose: 25% (12.5g/ 50 mL)) administrated in our dataset, the clinical characteristics of these two

albumin supplementation groups before and after PS matching according to the age, SOFA score, and complications, were shown in Table 4. Though it was not statistically significantly, a lower mortality rates (16.50% vs 24.27%), ICU LOS (4.00(2.23-8.58) vs 4.78(2.17-10)) and hospital LOS (11.91(7.21-19.5) vs 12.44(6.96-18.75)) were observed in the higher dose group.

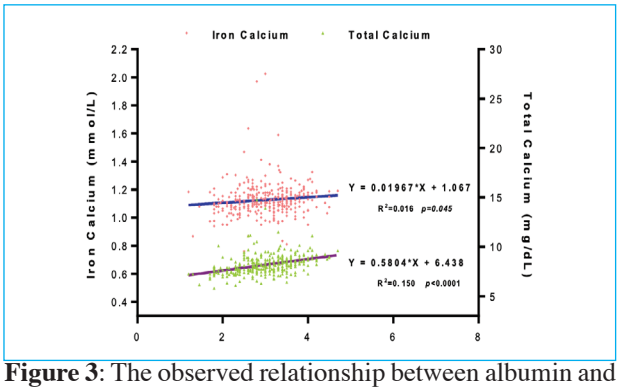

Figure 3: The observed relationship between albumin and total calcium and iron calcium in the septic patients at the time of first ICU admission.

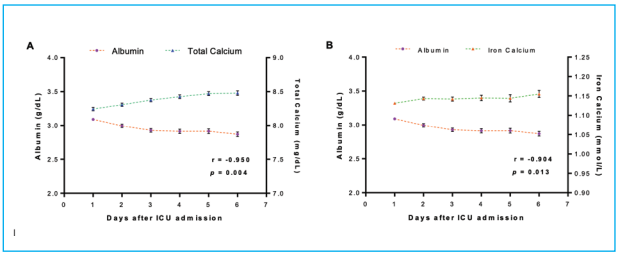

Figure 4: The relationship between albumin and total calcium and iron calcium in septic patients for the first 6 days after ICU admission.

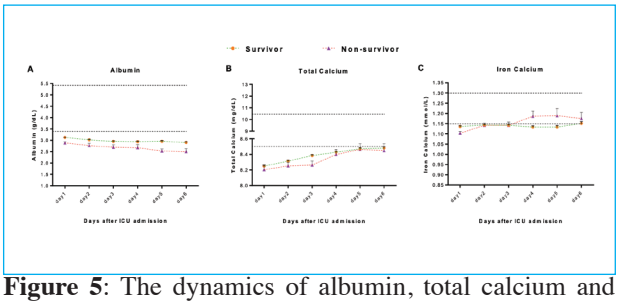

Figure 5: The dynamics of albumin, total calcium and iron calcium in survivor and non-survivor septic patients for 6 days after ICU admission.

To examine whether albumin supplementation has a potential effect on the total and iron calcium levels, the data of total and iron calcium levels were collected and compared on the day before, during, as well as after albumin administration, respectively. The result showed that a significantly lower levels of the total calcium were observed during and after the higher dose albumin supplementation (Figure 6A), however, no significantly change on the iron calcium level were seen (Figure 6C).

Similarly, there were no significant effects on both the total calcium (Figure 6B) and iron calcium (Figure 6D) levels when supplement with the lower dose of albumin. These results suggested that a higher dose of albumin might down-regulate the total calcium level and benefit the outcome.

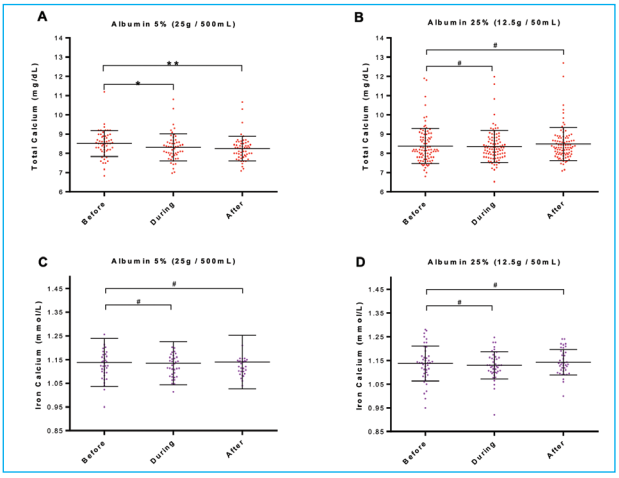

Figure 6: The possible effects of albumin supplementation on the serum total calcium and iron calcium. The effects of higher dose of albumin supplement on the serum total calcium (A) and iron containing calcium (C); The effects of the lower dose of albumin supplement on the total calcium (B) and serum iron calcium (D).

Discussion

Here we found that over 60% of patients were diagnosed with both hypoalbuminaemia and hypocalcaemia at the day of ICU admission, which was significantly higher than those who had hypoalbuminaemia or hypocalcaemia along, thereby suggesting that the incidences of hypoalbuminemia and hypocalcaemia is relatively common in sepsis. However, the correlation between the two of them and their combinatorial effects on the prognosis in sepsis is largely unknown. Our results showed that there was a negative correlation tendency between the serum albumin and calcium in the sepsis patients during their ICU stay. Importantly, hypocalcaemia might be protective in the septic patients under certain circumstances, particularly when patients were diagnosed with marked hypoalbuminemia. This study highlights the potential relationship between hypoalbuminemia and hypocalcemia in the sepsis, which might help early prognosis prediction and facilitate better clinical interventions against the serum albumin and calcium metabolic abnormalities.

The drop in the levels of albumin and calcium during sepsis might arise because of different mechanisms, but also in equilibrium with each other.

	Before Propensity Score Matching				After Propensity Score Matching		
	25%(12.5 g/ 50 mL) (n=132)	5%(25 g/500 mL) (n=193)	*P* value		Lower dose 25%(12.5 g/ 50 mL, n=103)	Higher dose 5%(25 g/500 mL; n=103)	*P* value
Age (years; median, Q_1~Q_3)	63.36(54.06-76.04)	68.01(59.52-77.88)	0.010		63(54-76)	63(54-71)	0.556
Male (male, %)	70(53.03%)	116(60.1%)	0.206		53(51.46%)	59(57.28%)	0.401
Race white (n, %)	105(79.55%)	138(71.5%)	0.101		83(80.58%)	70(67.96%)	0.038
Race black (n, %)	5(3.79%)	12(6.22%)	0.334		4(3.88%)	9(8.74%)	0.152
Race hispanic (n, %)	3(2.27%)	7(3.63%)	0.488		3(2.91%)	4(3.88%)	0.701
Race other (n, %)	19(14.39%)	36(18.65%)	0.315		13(12.62%)	20(19.42%)	0.184
Albumin level	2.761±0.720	2.577±0.637	0.158		2.65(2.16-3.2)	2.50(2.03-2.95)	0.423
Total Calcium	8.05(7.65-8.7)	8.00(7.6-8.5)	0.288		8.00(7.66-8.68)	8.03(7.59-8.55)	0.699
Iron Calcium	1.133(1.09-1.19)	1.124(1.09-1.18)	0.758		1.13(1.09-1.19)	1.12(1.09-1.17)	0.376
complications							
Congestive heart failure (n, %)	25(18.94%)	53(27.46%)	0.077		21(20.39%)	22(21.36%)	0.864
Cardiac arrhythmias (n, %)	41(31.06%)	91(47.15%)	0.004		32(31.07%)	24(23.3%)	0.210
Valvular disease (n, %)	10(7.58%)	28(14.51%)	0.056		8(7.77%)	13(12.62%)	0.250
Pulmonary circulation (n, %)	14(10.61%)	21(10.88%)	0.937		11(10.68%)	8(7.77%)	0.470
Peripheral vascular (n, %)	10(7.58%)	24(12.44%)	0.160		7(6.8%)	7(6.8%)	1.000
Hypertension (n, %)	72(54.55%)	125(64.77%)	0.064		57(55.34%)	56(54.37%)	0.889
Other neurological (n, %)	13(9.85%)	18(9.33%)	0.875		10(9.71%)	7(6.8%)	0.447
chronic_pulmonary (n, %)	32(24.24%)	43(22.28%)	0.680		26(25.24%)	16(15.53%)	0.084
diabetes_uncomplicated (n, %)	27(20.45%)	37(19.17%)	0.775		22(21.36%)	21(20.39%)	0.864
diabetes_complicated (n, %)	11(8.33%)	13(6.74%)	0.589		5(4.85%)	7(6.8%)	0.552
Hypothyroidism (n, %)	13(9.85%)	27(13.99%)	0.264		10(9.71%)	14(13.59%)	0.385
renal_failure (n, %)	32(24.24%)	31(16.06%)	0.067		25(24.27%)	19(18.45%)	0.308
liver_disease (n, %)	63(47.73%)	28(14.51%)	0.000		35(33.98%)	27(26.21%)	0.224
metastatic_cancer (n, %)	12(9.09%)	11(5.7%)	0.242		11(10.68%)	7(6.8%)	0.324
rheumatoid_arthritis (n, %)	5(3.79%)	12(6.22%)	0.334		3(2.91%)	7(6.8%)	0.195
Coagulopathy (n, %)	35(26.52%)	41(21.24%)	0.270		26(25.24%)	26(25.24%)	1.000
Obesity (n, %)	9(6.82%)	14(7.25%)	0.880		8(7.77%)	5(4.85%)	0.390
weight_loss (n, %)	17(12.88%)	12(6.22%)	0.039		9(8.74%)	8(7.77%)	0.800
fluid_electrolyte (n, %)	73(55.3%)	75(38.86%)	0.003		60(58.25%)	59(57.28%)	0.888
Severity							
Severe_sepsis_explicit (n, %)	24(18.18%)	29(15.03%)	0.449		20(19.42%)	23(22.33%)	0.607
Sepsis shock (n, %)	20(15.15%)	26(13.47%)	0.670		17(16.5%)	21(20.39%)	0.472
SOFA (mean±SD)	7(5-9)	6(4-9)	0.0377		7(5-10)	7(4-10)	0.735
ICU los (days; median Q_1~Q_3)	4.24(2.24-8.77)	3.64(2.22-7.85)	0.256		4.78(2.17-10)	4.00(2.23-8.58)	0.557
Hospital los (days; median Q_1~Q_3)	12.26(7.03-19.37)	10.85(7.04-17.42)	0.2550		12.44(6.96-18.75)	11.91(7.21-19.5)	0.969
Hospital death (n, %)	32(24.24%)	22(11.40%)	0.002		25(24.27%)	17(16.5%)	0.167

Table 4: The clinical characteristics between the survivors and non-survivors (hospital mortality) of sepsis patients without albumin and calcium supplementation.

SOFA, Sequential Organ Failure Assessment; ICU LOS, intensive care unit length of stay; Hospital LOS, Hospital length of stay.

Albumin is the major protein present in the plasma and constitutes approximately 60% of the plasma protein. It represents about 25% of total protein synthesized in the liver. Hypoalbuminaemia in septic patients may arise due to the liver damage or rapid loss of this protein from the intravascular space caused primarily by systemic capillary leakage process, which are the common pathological conditions found in sepsis. Thus, it is possible that the serum calcium level can be affected in the same way since a large part of serum, calcium is found in the complex with albumin, and a potential decrease in the total serum calcium can result from a reduction in serum albumin. However, the total calcium and iron calcium showed a similar pattern in changes in their levels, the iron calcium level might remain unchanged as it is precisely regulated, and therefore the clinical manifestations of the hypocalcaemia have been reported to be usually mild or

not obvious, thereby rendering the hypocalcaemia generally being underemphasized in these patients.

The occurrence of hypoalbuminemia has been often associated with hypocalcaemia during the critical illness and has been widely documented previously in several literatures. In conditions of hypoalbuminemia, not only the levels of the total calcium but also that of ionized calcium can be affected[14]. It has been reported previously that there was a positive correlation between the serum albumin level and ionized calcium in idiopathic nephritic syndrome[15]. Wilson et.al reported that there a significant hypoalbumineamic hypocalcaemia occurred in a 5-year old child who suffered from complicated 50% full-thickness burns. Imrie et.al reported the occurrence of low serum ionized calcium in acute pancreatitis because of hypoalbuminemia[16]. On the contrary, another study reported that severe hypoalbuminaemia could be possibly caused by low serum ionized calcium[17]. These studies have suggested that the hypoalbuminemia and hypocalcaemia may potentially interact with each other in several critical illnesses.

Nevertheless, the mechanisms underlying the potential interactions between the hypoalbuminaemia and hypocalcaemia are largely unknown, and only very few studies have investigated the correlation between the serum albumin and calcium in sepsis patients. We found that the septic patients who had both albumin and calcium supplement displayed a poorer prognosis as compared to others. The prognosis from the sepsis-related significantly to hypoalbuminemia, as a substantially higher SOFA score and mortality in patients with worse hypoalbuminaemia was noted, which was consistent with the previous evidence which demonstrated that both hypocalcaemia and hypoalbuminaemia can serve as an independent factor that could be directly associated with mortality in the critically ill patients. We hypothesize that a significantly greater risk of mortality will predominantly appear when marked hypoalbuminemia patients combined with those suffering from the marked hypocalcaemia. However, it was not the case, the highest mortality rate was seen in those patients who suffered from the severe hypoalbuminemia but had normal calcium levels, and the risk of death decreased significantly as the hypocalcaemia became worse. A number of the previously reported studies in critically ill patients have yielded conflicting results regarding the hypocalcaemia, and both moderate as well as the severe hypocalcaemia were associated with increased mortality, whereas mild hypercalcaemia was associated with significant lower mortality[7, 8, 18]. It could be possible that there can be potential positive and negative effects of hypocalcaemia on the mortality dependent on the degree of hypocalcaemia as well as that of the hypoalbuminaemia. We examined the change of the serum albumin and calcium in the septic patients who were without albumin and calcium replacement during their ICU stay. Interesting, both albumin and calcium levels were found to be in the normal range in the following days after ICU admission, but their dynamic trend was markedly difference. The level of albumin decreased gradually and the non-survivors had lower albumin levels compared to that in the survivors, while the both total and iron calcium levels tend to increase daily during the ICU stay, which probably can be attributed to the catabolism of body upon sepsis, and these disturbances in the metabolism might be worse in the non-survivors.

We believe that the hypocalcaemia might be potentially associated with a metabolic response that can be considered as an adaptive and related to the immune response, which might work on a similar principle of inflammation and fever, as both inflammation and fever in themselves are considered as the protective immune responses of body. However, If these activities too severe, these can aggravate and cause substantial harm to the body. Similarly, serious complications can be caused by severe hypocalcaemia. This may explain why patients with mild hypocalcaemia have the lowest mortality but turn out deteriorate when hypocalcaemia getting worse. One important question is that why the marked hypoalbuminemia patients with the normal total calcium level had the highest mortality rate, while the marked hypocalcaemia can serve as a protective mechanism when the septic patients suffer from marked hypoalbuminemia. Additionally, why the potential correlation between the hypocalcaemia and immune response might not be the same under different levels of the serum albumin or severity of disease remains to be investigated. We would not exclude the possibility that only patients with marked hypoalbuminemia but with the normal calcium level have been treated with calcium agent before ICU admission, which may cause potential bias in our conclusion. It had been recommended by some clinical investigators that patients should not be interfered with the early catabolic phase of critical illness by administering large amounts of any macronutrient[19], and less intensive interventions

might prove to be superior in some cases. The well know notion that "less is more" in ICU patients, may not only suitable for the nutritional supplements, but also maybe some kind of auto regulated protective mechanisms of body that can be stimulated upon a critical illness. The decrease of the serum calcium may work like the previously used bloodletting treatment, which was one of the most commonly employed medical practices performed by the surgeons from antiquity until the late 19th century, but has been abandoned nowadays, probably due to adverse effects on metabolism regulation.

Intravenous albumin administration has been widely used as a therapeutic agent in ICU for more than 50 years. Albumin can exhibit multiple e; ects. It can regulate the vascular properties by maintaining osmotic pressure and microvascular integrity; transport hormones, biliary salts, bilirubin, fatty acids, and ions like calcium; adjust acid-base balance; and exert significant anti-oxidative and anti-apoptotic e; ects[20-22]. Despite plausible reasons for the use of albumin, previous studies about albumin supplementation have yielded controversial results. Many trials have failed to show favorable evidence based data supporting its routine use[23, 24]. However, one important bias may exist as there is a tendency to generally administer albumin to more severely ill patients, therefore a false association between a higher dose of albumin and increased mortality rates were observed.

The diverse dynamics of albumin and calcium (both total and iron calcium) during the ICU stay, clearly suggest that a possible interaction between the disturbance of albumin and calcium during sepsis may exist, which can possibly explain the effect of combination of this two mineral disturbance on the prognosis of this disease. We examined the change in the calcium level after administration of the different doses of albumin and found that the higher dose of albumin can down-regulate the total calcium but not the iron calcium level, and a lower mortality were also seen in those patients. On the contrary, the lower dose of albumin had no significant effect on the calcium level. This finding implied that higher dose of albumin supplementation can markedly benefit the prognosis as compared to the lower dose one. However, we did not observe any change in the iron calcium after this intervention, probably due to the presence of a large amount of iron calcium data sensor. Additionally, consistent with above results, the decrease in the total calcium level may counteract the adverse effects of severe hypoalbuminemia by unknown mechanisms, and a higher dose of albumin may not only up-regulate the serum albumin level but also can effectively down-regulate the total calcium level, and therefore improve the clinical outcome. Whatever the correct explanation of the association might be, further studies to identify the combination of albumin and calcium at different levels in sepsis patients and elucidating the underlying mechanisms of actions will clearly benefit the clinical decision making process for individual patients.

There are several limitations associated with this study. First, it was retrospective study based on an ICU database, therefore could not systematically exclude the patients who have received albumin and calcium supplementation prior to admission to the ICU that may have cause potential bias to our results. Second, our approach did not thoroughly investigate the time window of albumin and calcium supplementation as it was difficult to determine because the time of administration and duration varied largely from case to case. Third, the dynamics of albumin and calcium could change rapidly and hence our primary focus only on the albumin and calcium status on the first day of ICU admission might be inadequate. Finally, there were many data sensors, particularly the ironed calcium data, rendering the study insignificant to provide convincing conclusions to some of the findings in our study.

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Corresponding Author:
Wencheng He
Email: hewenchengsg@163.com
(China)