Calcium supplementation prolongs the time of hospitalization and has a double effect on mortality in septic patients: A retrospective study from MIMIC-III

Wencheng He
Peking University Shenzhen Hospital
Youzhong An
Peking University Shenzhen Hospital
Lei Huang
Peking University Shenzhen Hospital
Hua Luo
Peking University Shenzhen Hospital
Jingying Chen
Peking University Shenzhen Hospital
Weijia Li
Peking University Shenzhen Hospital
Yiming Zhang
Peking University Shenzhen Hospital
Weixing Zhang (zhangwx@hotmail.com)

Research

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Abstract

Background Hypocalcemia is a common electrolyte disturbance in sepsis, calcium administration in those patients remains a controversial issue. The aim of this study was to assess the association of calcium supplementation with the time of hospitalization and mortality in septic patients.

Method 5761 eligible septic patients, including 2689 with calcium supplementation and 3072 without calcium supplementation, were extracted from the MIMIC-III database. A total of 1463 pair patients were included in the analysis after propensity score matching according to the age, sex, SOFA score and lactate on first ICU admission. We compared the length of stay (LOS) in the intensive care unit (ICU) and hospital, as well as the 28-day and hospital mortality, which stratified the analysis according to the Sequential Organ Failure Assessment (SOFA) score, and the iCa on the first ICU admission between the matched groups.

Results The results showed that either a too-low or a too-high iCa increased the risk for septic patients, but the minimum of the mortality curve in the non-calcium supplement group was locally in the mild hypocalcemia range. Regardless of the SOFA score and iCa, the LOS in both the ICU and hospital were higher in the calcium supplement group than in the non-calcium supplement group. Overall, the 28-day and hospital mortality were greater but not statistically significant in the calcium supplement group than in the non-calcium supplement group (14.83% vs 13.39%, p=0.416; 16.20% vs 13.88%, p=0.079, respectively). However, the survival analysis stratified by SOFA score showed that calcium supplementation reduced mortality when the patient's SOFA score was >8 (p=0.028), while it worsen the outcome when the SOFA score was ≤4 (p<0.001) and had no significant effect with SOFA scores from 5~8 (p=0.556).

Conclusion Our findings suggest that mild hypocalcemia may be protective in septic patients and that calcium supplementation may prolong hospitalization and have a double effect on mortality. The SOFA score may be a valuable clinical index for calcium administration decision making.

Introduction

Hypocalcemia has been widely recognized as a biochemical abnormality in critically ill patients[1, 2], septic patients are at particular risk of hypocalcemia[3, 4]. The etiology of hypocalcemia has been extensively researched in septic patients[5, 6], and many factors, such as decreased parathyroid hormone (PTH) release, tissue calcium accumulation, iCa release into ascites fluid, and hypomagnesemia, are thought to be involved in causing hypocalcemia during sepsis. Nevertheless, which is the major factor that causes hypocalcemia in sepsis is still not clear, and more than half of patients in the ICU have no identifiable etiology for hypocalcemia.

iCa acts as a ubiquitous intracellular messenger and coenzyme throughout the body. Without adequate calcium regulation, the body ceases to function properly, and many different clinical signs can be seen[7]. Hypocalcemia has been found to be associated with poor outcomes in septic patients[8–10]. Patients with severe hypocalcemia who fail to recover their normal iCa in an early state have significantly higher mortality[2]. It has been recommended that calcium should be replaced to prevent life-threatening complications such as laryngospasm, tetany, seizures and cardiac abnormalities[11, 12]. However, the treatment of hypocalcemia in critically ill patients remains a controversial issue[13]. We still lack evidence-based guidance since no randomized controlled trial has been conducted to evaluate the effect of calcium administration on prognosis in septic patients. Studies in critically ill patients have also yielded conflicting results regarding calcium supplementation. One large retrospective study showed that calcium supplementation can improve the 28-day and 90-day survival in ICU patients[14]. However, several clinical observation studies have shown that calcium supplementation in critically ill patients provides no benefit or even worsen outcomes[15, 16]; moreover, experiments using an animal model of sepsis showed that calcium administration increases mortality[17].

Considering that heterogeneity is common in septic patients, previous studies did not stratify patients according to the severity of the hypocalcemia and disease, and we thus wondered whether the effect of calcium administration may vary from

case by case. Herein, we conducted a retrospective study by extracting septic patient data from MIMIC- to evaluate whether calcium supplementation should be administered and under which condition it is suitable for septic patents.

Methods

Design

This study aimed to investigate the effect of calcium supplementation on the prognosis of septic patients. First, factors including age, sex, iCa and lactate on first ICU admission, and other complications were examined for their association with hospital mortality in septic patients. Then, the prognostic differences between the calcium supplement and non-calcium supplement groups were stratify analyzed according to the iCa on first ICU admission and SOFA scores. Finally, the range of iCa and SOFA scores that worsened or benefited the outcome were examined by survival analysis.

Database

This was a single-center, retrospective, observational study. We employed the Medical Information Mart for Intensive Care III (MIMIC-III, latest version 1.4) database. MIMIC-III is an open, publicly available ICU database that is composed of clinical data and physiological waveforms. The database contains records from 53,423 deidentified ICU patients admitted to Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA) from 2001 to 2012. The database contains records of demographics, intravenous (IV) medications, laboratory results, nursing progress notes, fluid balance, and other clinical variables. Our access to the database was approved after completion of the CITI program course named “Human Research-Data or Specimens Only Research” (Record ID: 31532119). The project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and informed consent was waived due to the purely observational nature of the study. This study was approved by the ethics committee of Peking University Shenzhen Hospital.

Cohort Selection

The extraction of septic patients was performed according to the method reported by Alistair et al., which closely adhered to the Sepsis-3 definition[18]. The queries were stored on a public repository-GitHub (https://github.com/alistairewj/sepsis3-mimic/tree/master/query). As the explicit sepsis codes were introduced at BIDMC in 2004 and the group of admissions between 2008 and 2012 were easily identifiable in the database, only ICU admissions from 2008 to 2012 (n = 23,620) were enrolled in the present study; among them, the admission included 3 nonadults, 7,536 secondary (or greater) admissions (to avoid repeated measures), 2,298 patients who experienced cardiothoracic surgery (their postoperative physiologic derangements did not translate to the same mortality risk as the other ICU patients), 1,974 suspected of infection more than 24 hours before and after ICU admission (as MIMIC-III only contains ICU data, we chose to focus on the majority of patients who were admitted to the ICU with sepsis to ensure independence between data points), 6,030 patients who had a SOFA score lower than 2 and were noninfectious, and 18 patients with missing data were excluded. The final cohort contained 5761 patients, including 2689 patients with calcium supplementation and 3072 patients without calcium supplementation (Fig. 1). The data extraction was executed by using PostgreSQL (version 4.6).

Statistical Analysis

The normality of the distribution of continuous variables was tested by using the Kolmogorov–Smirnov test. Data with a normal distribution are expressed as the mean ± SD and compared using Student’s T test; otherwise, data are expressed as the median with interquartile range and were compared using the Mann-Whitney U test. Categorical variables are expressed as percentages and were compared using the Chi square test. Variables between survivors and nonsurvivors were compared by using a univariate analysis to screen the potential risk factors associated with hospital mortality. Covariates with $p < 0.1$ in

the single factor analysis were included in binary logistic regression analysis to investigate the significant risk factors associated with hospital mortality.

The LOS in the ICU and hospital between the calcium supplement and non-calcium supplement cohorts were compared using multiple comparisons. To investigate which particular situations are suitable or not for calcium supplementation, each interval in the stratified analysis was evaluated according to the intersections of the mortality curves of the two matching groups. The SOFA scores were categorized into the following intervals: <5, 5 ~ 8, and > 8. The iCa was categorized into the following intervals: <0.9, 0.90 ~ 1.20, and > 1.20 mmol/L. The survival analysis of calcium supplement and non-calcium supplement cohorts in each interval was performed by landmark survival analysis to determine the effect of calcium supplementation on hospital mortality. Kaplan–Meier survival curves are depicted.

The statistical analyses were performed using the software IBM SPSS statistic (vision 25). Two-tailed $p < 0.05$ was considered to indicate a statistically significant difference.

Results

1. iCa on first ICU admission is correlated with mortality in septic patients

A total of 5761 ICU admissions satisfied our inclusion criteria and were included in our analysis. Of those, 2694 patients had iCa records on first ICU admission, of whom 1,889 (70.12%) patients had hypocalcemia(iCa <1.15 mmol/L), 716 (26.58%) patients had a normal iCa range (1.15 ≤ iCa ≤ 1.30 mmol/L), and 89 (3.30%) patients had hypercalcemia (iCa > 1.30 mmol/L) (Table 1). There were 4,929 survivors and 832 nonsurvivors during the hospital stay (mortality: 14.44%) (Table 2). Factors associated with hospital mortality were examined. The nonsurvivors were significantly older than the survivors (69.26 (55.02~80.55) vs 63.61 (51.72~75.70), p<0.001). The iCa on first ICU admission was significantly lower in nonsurvivors than in survivors (1.09 (1.00~1.14) vs 1.10 (1.04~1.15), p=0.006). The lactate on first ICU admission was significantly higher in nonsurvivors than in survivors (2.80 (1.70~5.50) vs 1.70 (1.20~2.60), p<0.001). There were more patients with congestive heart failure (27.76% vs 24.57%, p=0.047), cardiac arrhythmias (46.87% vs 34.94%, p<0.001), renal failure (22.00% vs 19.37%, p=0.080), liver disease (27.04% vs 13.84%, p<0.001), metastatic cancer (12.86% vs 5.84%, p<0.001), coagulopathy (27.28% vs 15.75%, p<0.001), and fluid electrolyte (64.42% vs 43.83%, p<0.001) in nonsurvivors than in survivors. Variables with p<0.1 were entered into a binary regression model, which showed that age (OR: 1.037; 95% CI: 1.024~1.025), iCa on first ICU admission (OR: 0.263; 95% CI: 0.072~0.958), lactate on first ICU admission (OR: 1.404; 95% CI: 1.296~1.521), cardiac arrhythmias (OR: 1.867; 95% CI: 1.304~2.673), liver disease (OR: 1.798; 95% CI: 1.142~2.831), metastatic cancer (OR: 3.372; 95% CI: 1.931~5.891), and fluid electrolytes (OR: 1.867; 95% CI: 1.304~2.673) were associated with hospital mortality in septic patients (Table 3), among these, the decrease in the iCa on first ICU admission posed an increased risk of mortality.

2. Calcium Supplementation Prolongs Hospitalization In Septic Patients

There were 2,689 (46.68%) admissions with calcium supplementation and 3,072 (53.32%) without calcium supplementation during the ICU stay. Calcium gluconate (n = 2,362, 83.36%) and calcium carbonate (n = 439, 16.33%) were the two major sources of calcium supplementation. After propensity score matching according to age, sex, SOFA score and lactate on first ICU admission, 1463 pairs of patients were included in the analysis (Table 4). Of these, 939 had an iCa record on first ICU admission in calcium supplement group, while 589 had an iCa record on first ICU admission in the non-calcium supplement group.

Overall, the LOS of the ICU was significantly higher in the calcium supplement group than in the non-calcium supplement group (3.38 (1.89 ~ 7.42) vs 2.02 (1.23 ~ 3.66), p < 0.001), and similar results were also seen in the LOS of hospital (8.88

(5.56 ~ 14.69) vs 6.54 (3.82 ~ 10.66), p < 0.001) (Table 4). To examine whether the effect of calcium supplementation on hospitalization may vary according to the severity of the disease, we stratified patients according to the SOFA score and iCa on first ICU admission, respectively. The results showed that regardless of the SOFA score and iCa, the LOS in both the ICU (Fig. 2A and Fig. 4A) and hospital (Fig. 2B and Fig. 4B) were higher in the calcium supplement group than in the non-calcium supplement group, although some intervals showed no significant difference between the matching groups. These results suggest that calcium supplementation prolongs hospitalization in septic patients.

3. Calcium supplementation had a double effect on the mortality of septic patients

We compared the mortality curves between the calcium supplement group and the non-calcium supplement group by stratifying analysis as described above. There are crosses between the two mortality curves of the matching groups.

In the matching group stratified by iCa, the mortality of the matching groups in each iCa interval is shown in Table 5. Overall, the 28-day and hospital mortality in the calcium supplement group was higher than that in non-calcium supplement group (17.03% vs 15.96%, 18.32% vs 16.25%, respectively). We depicted the mortality curve in both 28-day (Fig. 2C) and hospital (Fig. 2D) patients, which, according to each interval, showed a U-shape, which means that either a too high or too low iCa would be an increased risk for septic patients. However, from this regression curve, we found that the minimum of this curve (approximately 1.00 mmol/L) was located in the mild hypocalcemia interval but not the normal iCa range, while giving a calcium supplement in this interval would increase the mortality. This was confirmed by the landmark analysis, which showed that administering calcium supplementation to the patients who had an iCa within 0.90 ~ 1.20 mmol/L yielded a lower survival rate at the later stage of disease (p = 0.029) (Fig. 3). These results suggest that mild hypocalcemia may be protective. In contrast, when the patient's iCa was lower than 0.90 or higher than 1.20 mmol/L, a lower mortality was observed. However, the survival analysis showed no significant difference between the matching groups in those intervals (Fig. 3).

In the matching groups stratified by SOFA score, the mortality at 28 days (Fig. 4C) and in the hospital (Fig. 4D) presented a progressive increase as the SOFA score increased. The difference of 28-day and hospital mortality between the matching groups were no longer significant after propensity score matching (14.83% vs 13.39%, p = 0.416, 18.32% vs 16.25%, p = 0.079, respectively)(Table 4). However, the result of survival analysis showed that calcium supplementation reduced the mortality when the patient's SOFA score was > 8 (p = 0.028), while a higher mortality was seen with calcium supplementation when the SOFA score was ≤ 4 (p < 0.001), and there was no significant difference when the SOFA score was within the range of 5 ~ 8 (p = 0.556) (Fig. 5), indicating that calcium supplementation has the opposite effect on mortality when patients under different severity of disease.

Table 1

The clinical characteristics of septic patients with different levels of iCa on the first ICU admission

Clinical parameters	Total (n = 2,694)	Hypocalcemia (< 1.15 mmol/L; n = 1,889, 70.12%)	Normal (1.15 ~ 1.30 mmol/L; n = 716, 26.58%)	Hypercalcemia (> 1.30 mmol/L; n = 89, 3.30%)	P value
Age (years; median, Q_1 ~ Q_3)	64.40(52.05 ~ 77.19)	63.39(50.82 ~ 76.56)	66.92(56.45 ~ 78.30)	64.31(53.87 ~ 80.51)	< 0.0001
Sex (male; n, %)	1579(58.61)	1099(58.18)	427(59.64)	53(59.55)	0.783
Ethnicity (n, %)					
White	1905(70.71)	1312(69.45)	534(74.58)	59(66.29)	0.024
Black	197(7.31)	131(6.93)	56(7.82)	10(11.24)	0.260
Hispanic/Latino	79(2.93)	67(3.54)	9(1.26)	3(3.37)	0.008
Other	513(19.04)	379(20.06)	117(16.34)	17(19.10)	0.097
Severity					
SOFA (mean ± SD)	6.33 ± 3.66	6.47 ± 3.80	5.84 ± 3.19	7.23 ± 3.87	0.0011
sirs (mean ± SD)	3.09 ± 0.87	3.13 ± 0.87	3.00 ± 0.86	3.00 ± 1.03	0.070
lods (mean ± SD)	5.66 ± 3.16	5.71 ± 3.25	5.41 ± 2.86	6.62 ± 3.47	0.020
qsofa (mean ± SD)	1.98 ± 0.67	1.96 ± 0.67	2.00 ± 0.68	2.05 ± 0.67	0.370
Septic shock (n, %)	423(15.70)	339(17.94)	74(10.34)	10(11.24)	< 0.0001
Vent (n, %)	1998(74.16)	1388(73.47)	542(75.70)	68(76.64)	0.455
Lactate (median, Q_1 ~ Q_3)	1.90(1.20 ~ 3.10)	1.90(1.30 ~ 3.22)	1.70(1.10 ~ 2.60)	3.10(1.80 ~ 5.40)	< 0.0001
28-day mortality (n, %)	478(17.74)	354(18.74)	104(14.53)	20(22.47)	0.008
Hospital mortality (n, %)	500(18.53)	371(19.64)	109(15.22)	20(22.47)	0.006
ICU LOS (days; median, Q_1 ~ Q_3)	3.37(1.86 ~ 7.27)	3.57(1.90 ~ 7.79)	3.10(1.66 ~ 6.23)	2.84(1.761 ~ 5.68)	0.0023
Hospital LOS (days; median, Q_1 ~ Q_3)	8.98(5.44 ~ 15.01)	8.97(5.36 ~ 15.44)	8.95(5.71 ~ 13.87)	9.69(5.16 ~ 13.66)	0.861

Table 2

Differences in clinical characteristics between survivors and nonsurvivors (hospital mortality)

	Total (n = 5761)	Survivors (n = 4929)	Nonsurvivors (n = 832)	Chi Square/Z	P
Age (median IQR)	66.97(53.90 ~ 79.92)	63.61(51.72 ~ 75.70)	69.26(55.02 ~ 80.55)	-8.677	< 0.001
Sex (male; n, %)	3213(55.77)	2759(55.97)	454(54.56)	0.572	0.450
Ca^{2+} on first ICU admission (median, $Q_1 \sim Q_3$)	1.10(1.04 ~ 1.15)	1.10(1.04 ~ 1.15)	1.09(1.00 ~ 1.14)	-2.734	0.006
Lactate on first ICU admission (median, $Q_1 \sim Q_3$)	1.8(1.2–2.8)	1.70(1.20 ~ 2.60)	2.80(1.70 ~ 5.50)	-12.615	< 0.001
Congestive heart failure (n, %)	1442(25.03)	1211(24.57)	231(27.76)	3.861	0.049
Cardiac arrhythmias (n, %)	2112(36.37)	1722(34.94)	390(46.87)	43.640	< 0.001
Pulmonary circulation (n, %)	467(8.11)	391(7.93)	76(9.13)	1.377	0.241
Hypertension (n, %)	3365(58.41)	2880(58.42)	485(58.29)	0.005	0.941
Chronic pulmonary (n, %)	1377(23.91)	1156(23.46)	221(26.56)	3.772	0.052
Diabetes uncomplicated (n, %)	1235(21.45)	1055(21.40)	180(21.63)	0.022	0.881
Diabetes complicated (n, 3%)	375(6.51)	325(6.60)	50(6.01)	0.401	0.527
Hypothyroidism (n, %)	733(12.72)	617(12.52)	116(13.94)	1.296	0.255
Renal failure (n, %)	1138(19.75)	955(19.37)	183(22.00)	3.073	0.080
Liver disease (n, %)	907(15.74)	682(13.84)	225(27.04)	93.542	< 0.001
Metastatic cancer (n, %)	395(6.85)	288(5.84)	107(12.86)	54.863	< 0.001
Coagulopathy (n, %)	1003(17.41)	776(15.75)	227(27.28)	65.881	< 0.001
Fluid electrolyte disturbance (n, %)	2696(46.81)	2160(43.83)	536(64.42)	121.227	< 0.001

Table 3

Binary logistic regression analysis showing variables associated with hospital mortality

	B	S.E.	Wald	Sig.	OR	95% CI for OR	
						Lower	Upper
Age	0.036	0.006	32.292	< 0.001	1.037	1.024	1.050
iCa on first ICU admission	-1.335	0.659	4.103	0.043	0.263	0.072	0.958
Lactate on first ICU admission	0.339	0.041	69.373	< 0.001	1.404	1.296	1.521
Congestive heart failure	0.007	0.228	0.001	0.974	1.007	0.644	1.575
Cardiac arrhythmias	0.783	0.196	16.045	< 0.001	2.189	1.492	3.211
Chronic pulmonary	0.374	0.206	3.290	0.070	1.454	0.970	2.179
Renal failure	0.044	0.247	0.031	0.859	1.045	0.643	1.696
Liver disease	0.586	0.232	6.408	0.011	1.798	1.142	2.831
Metastatic cancer	1.216	0.285	18.250	< 0.001	3.372	1.931	5.891
Coagulopathy	0.369	0.212	3.049	0.081	1.447	0.956	2.190
Fluid electrolyte disturbance	0.624	0.183	11.645	0.001	1.867	1.304	2.673

Table 4

The clinical characteristics of septic patients with or without calcium supplementation (before and after propensity score matching)

Clinical parameters	Before propensity score-matched			After propensity score-matched		
	Calcium supplementation (n = 2,689)	Non-calcium supplementation (n = 3,072)	P value	Calcium supplementation (n = 1,463)	Non-calcium supplementation (n = 1,463)	P value
Age (years; median, $Q_1 \sim Q_3$)	64.85(52.01–77.82)	68.77(55.95–81.51)	< 0.001	66.64(53.50 ~ 79.09)	66.67(54.64 ~ 80.11)	0.225
Sex (male, %)	1541(57.31)	1672(54.43)	0.013	801(54.75)	781(53.38)	0.458
Lactate on first hospital admission (median, $Q_1 \sim Q_3$)	1.90(1.30 ~ 3.10)	1.70(1.2 ~ 2.5)	< 0.001	1.80(1.20 ~ 2.80)	1.80(1.3 ~ 2.6)	0.757
iCa on first ICU admission (mmol/L)	1.10(1.03 ~ 1.15)	1.12(1.06 ~ 1.17)	< 0.001	1.10(1.03 ~ 1.15)	1.11(1.05 ~ 1.17)	0.007
Ethnicity (n, %)						
White	1907(70.92)	2273(74.00)	0.845	1040(71.09)	1063(72.69)	0.344
Black	214(7.96)	291(9.47)	0.051	110(7.52)	153(10.46)	0.005
Hispanic/Latino	91(3.38)	96(3.13)	0.055	59(4.03)	53(3.62)	0.563
Other	477(17.74)	412(13.41)	< 0.001	254(17.36)	194(13.26)	0.002
Metastatic_cancer	148(5.50)	193(6.28)	0.236	98(6.70)	97(6.63)	0.941
Diabetes	758(28.19)	870(28.32)	0.959	418(28.57)	418(28.57)	1.00
Severity						
SOFA (mean ± SD)	6.05 ± 3.611	4.85 ± 2.71	< 0.001	5.43 ± 2.97	5.40 ± 2.89	0.767
sirs (mean ± SD)	3.05 ± 0.89	2.79 ± 0.94	< 0.001	3.06 ± 0.87	2.90 ± 0.90	< 0.001
lods (mean ± SD)	5.39 ± 3.10	4.54 ± 2.66	< 0.001	5.39 ± 3.10	4.54 ± 2.66	< 0.001
qsofa (mean ± SD)	1.96 ± 0.66	1.86 ± 0.73	< 0.001	1.94 ± 0.65	1.92 ± 0.71	0.313
Sepsis shock (n, %)	472(17.55%)	266(8.66%)	< 0.001	255(17.43)	181(12.37)	< 0.001
Vent (n, %)	1659(61.70%)	1120(36.46%)	< 0.001	824(56.33)	562(38.41)	< 0.001
28-day mortality (n, %)	442(16.43)	352(11.46%)	0.005	217(14.83)	196(13.39)	0.416
Hospital mortality (n, %)	471(17.52)	361(11.75%)	< 0.001	237(16.20)	203(13.88)	0.079

Clinical parameters	Before propensity score-matched			After propensity score-matched		
	Calcium supplementation (n = 2,689)	Non-calcium supplementation (n = 3,072)	P value	Calcium supplementation (n = 1,463)	Non-calcium supplementation (n = 1,463)	P value
ICU LOS (days; median Q_1 ~ Q_3)	3.65(1.87–7.97)	2.01(1.12–3.64)	< 0.001	3.38(1.89 ~ 7.42)	2.02(1.23 ~ 3.66)	< 0.001
Hospital LOS (days; median; Q_1 ~ Q_3)	8.99(5.54–15.67)	6.57(3.84–10.59)	< 0.001	8.88(5.56 ~ 14.69)	6.54(3.82 ~ 10.66)	< 0.001

Table 5
The difference in 28-day and hospital mortality in septic patients with or without calcium supplementation under different iCa intervals

iCa range (mmol/L)	Calcium supplementation (n = 939)			Non-calcium supplementation (n = 589)		
	iCa on first ICU admission (median, Q_1 ~ Q_3)	28-day Mortality(%)	Hospital mortality(%)	iCa on first ICU admission (median, Q_1 ~ Q_3)	28-day Mortality(%)	Hospital mortality(%)
≤ 0.90	0.84(0.79 ~ 0.89)	25.00	26.79	0.87(0.78 ~ 0.90)	42.11	47.37
0.91 ~ 1.00	0.97(0.94 ~ 0.99)	19.42	20.39	0.98(0.95 ~ 1.00)	13.64	13.65
1.01 ~ 1.10	1.07(1.04 ~ 1.09)	18.01	18.84	1.07(1.04 ~ 1.09)	15.08	15.08
1.11 ~ 1.20	1.14(1.12 ~ 1.17)	16.13	17.74	1.15(1.13 ~ 1.17)	14.47	14.47
1.21 ~ 1.30	1.25(1.22 ~ 1.27)	7.95	9.09	1.24(1.22 ~ 1.26)	14.28	15.58
> 1.30	1.40(1.33 ~ 1.55)	19.05	23.81	1.47(1.33 ~ 1.64)	33.33	33.33
Total	1.09(1.03 ~ 1.15)	17.03	18.32	1.12(1.06 ~ 1.17)	15.96	16.25

Discussion

Treatment of hypocalcemia in septic patients remains a controversial issue. The international guidelines developed by the Surviving Sepsis Campaign have no recommendation for calcium administration as a therapeutic measure[19]. However, we still lack evidence-based guidance since no randomized controlled trial has investigated whether calcium supplementation should be given to septic patients[13]. Unlike previous studies, our investigation assessed the prognosis of septic patients with or without calcium supplementation by stratified analysis of the iCa and SOFA scores. We found that calcium supplementation prolonged the time of hospitalization and had a double effect on mortality depending on the severity of the disease.

The morality curve in non-calcium supplement patients stratified by iCa intervals showed a U-shape, implying that abnormal iCa poses a risk to septic patients. Because hypocalcemia is more prevalent among septic patients than hypercalcemia is (in

our case, 70.12% vs 3.30%) and patients with severe hypocalcemia require critical care for a longer period[2], thus, hypocalcemia would be another prognostic marker of sepsis. Nevertheless, we found that the minimum point of this mortality curve was located at the mild hypocalcemia interval but not at the normal iCa range, suggesting that patients maintained under mild hypocalcemia may gain a benefit in outcome. Our recently experiment using septic model also showed that the mouse pre-treated with EDTA-2Na before the cecal ligation and punctuation (CLP)-operation, had 20 ~ 50% lower mortality compared with the non-EDTA-2Na treatment group (unpublished data). Despite these finding, whether the iCa change in blood is a protective mechanism or simply a consequence of metabolic dysregulation when the body undergoes a critical illness remains to be established. If the former is true, calcium supplementation may increase the burden of the body, which would attempt to downregulate the iCa and therefore worsen the outcome. Overall, the LOS in the ICU and hospital in septic patients with calcium supplementation was higher than that in the non-calcium supplement group. To examine whether the LOS may vary under different subranges of iCa and severity of disease, we stratified the LOS according to the iCa and SOFA scores. Nevertheless, the LOS tended to be higher in nearly all subranges of the calcium treatment group, suggesting that patients with calcium supplementation, longer stays in the hospital are caused by calcium treatment instead of the difference in iCa and severity of cases. In addition to septic patients, critically ill patients with calcium supplementation tend to stay longer in the hospital. One retrospective analysis of the effect of calcium treatment on critically ill patients showed that their LOS in both the ICU and hospital was longer than that of the non-calcium supplement group (3.25 (1.89 ~ 7.04) vs 1.79 (0.96 ~ 3.19), $p < 0.001$; 10 (6 ~ 17) vs 6 (4 ~ 12), $p < 0.001$, respectively), although a lower mortality was observed in the calcium supplement group[14].

Unlike hospitalization, there were crosses between the two mortality curves, suggesting that calcium supplementation has the opposite effect from case by case. It would be valuable for clinical decision making to determine which situation is suitable for calcium supplementation. Therefore, the intersection of the mortality curves was calculated, and we found that patients with calcium supplementation tended to have a higher hospital mortality when their iCa on first ICU admission was approximately 0.94 ~ 1.16 mmol/L, suggesting that attempted blood calcium correction at this interval would be harmful. Because the majority of septic patients' iCa on the first ICU admission was located at this iCa interval, this may explain why some studies revealed that calcium supplementation has an adverse effect on the prognosis of septic patients[16, 20] and septic model[21, 22]. However, on the contrary, there is a trend showing that calcium supplementation decreased mortality when iCa on the first ICU admission was lower than 0.9 mmol/L and higher than 1.20 mmol/L, although we would not confirm this finding in the survival analysis, probably due to the small number of patients in those subgroups.

The double effect of calcium supplementation was significant when the patients were stratified according to the SOFA score. From this perspective, taking the SOFA score as a reference index for clinical decision making would be valuable. Although the SOFA score is not a routine clinical reference index for calcium administration. However, the incidence of severe hypocalcemia tends to be more pervasive in severe septic cases, as a negative correlation between iCa concentration and mortality was observed in our and previously studies[9, 10]. Moritoki et al. reported that iCa concentration has no independent association with mortality and only extreme abnormalities of iCa are independent predictors of mortality[23]. In keeping with these results, it might be more convincing to say that calcium supplementation would benefit the outcome when the SOFA score is > 8 as well as when patient under severe hypocalcemia.

The underlying mechanism of the double effect of calcium supplementation in septic patients is not well illustrated. On the one hand, calcium supplementation administered to patients with severe hypocalcemia may avoid life-threatening complications such as cardiac arrest or seizures, which may explain why patients with iCa levels lower than 0.90 mmol/L have the highest mortality compared with patients with other iCa ranges. In addition, iCa also plays an important role in maintaining hemodynamics[24], and a direct relationship between iCa and arterial pressure has been found in critically ill patients[25]. It has also been reported that calcium supplementation may improve hemodynamics by increasing the mean arterial pressure (MAP), left ventricular stroke work index, and CO in critically ill patients[26, 27] and may improve heart function[28]. On the other hand, calcium supplementation can be deleterious at the cellular level because iCa may shifts into cells[29–31], giving additional parenteral calcium could therefore potentially aggregate the accumulation of cytosolic iCa concentrations, which would over activate pathways and generate reactive oxygen species that finally trigger cell death[32].

Studies using calcium blockers as a treatment for sepsis showed an improvement in the outcome[33–35], supporting this notion.

Therefore, the advantages and disadvantages should be weighed before calcium supplementation to the patient. Interestingly, our study showed that given calcium supplementation to patients with iCa on first ICU admission, more than 1.20 mmol/L tended to result in less mortality, as too high of an iCa level is also an increased risk factor for mortality in sepsis. However, it is important to note that although hypocalcemia is very common in septic patients, there are still a certain number of patients who do not present with hypocalcemia even though their SOFA scores are relatively high. Is it possible that these patients do not have an iCa influx problem? If so, it would be valuable to examine the contribution of calcium supplementation to hemodynamics in those individuals.

There are several limitations in this study. First, it was retrospective and purely observational. In particular, some patients who may have received calcium supplementation prior to admission to the ICU were not included in the analysis. Second, the dynamic of iCa could be fast-changing, both hypo- and hypercalcemia may present at one patient during the ICU stay[10], our study only focus on the iCa on the first ICU admission may be inadequate, despite we found it correlated with mortality in septic patients. In addition, the sample size of patients with iCa < 0.90 or > 1.20 mmol/L was small, also rendering the study underpowered to produce convincing conclusions in this subgroup. Third, our approach did not investigate the interactions with other factors associated with prognosis in sepsis. Finally, our study only presented a rough reference range of iCa and SOFA scores for calcium supplementation; greater amounts of data are required, and controlled intervention research should be performed to assess the accurate range to which this intervention should be applied for clinical decision making.

Conclusions

Septic patients are at particular risk of hypocalcemia, the effect of calcium administration on different severity of septic patients is largely unknown. We extracted septic patient's data from the MIMIC-III database and compared the prognosis between the calcium supplement and non-calcium supplement patients. Our finding suggest that mild hypocalcemia may be protective in septic patients. Although calcium supplementation may prolong hospitalization, a double effect of calcium supplement on mortality were observed after patients were stratified according to the SOFA score. Thus, the SOFA score may be a valuable clinical index for calcium administration decision making. Nevertheless, further controlled intervention research should be performed to verify the benefit and unfavorable effect of this intervention and apply it in clinical decision making.

Abbreviations

MIMIC-III	Medical Information Mart for Intensive Care III
BIDMC	Beth Israel Deaconess Medical Center
ICU	Intensive care unit
iCa	Ionic Calcium
SOFA	Organ Failure Assessment
CI	Confidence interval
OR	Odds ratio
MAP	Mean arterial pressure
CLP	Cecal ligation and punctuation
IV	intravenous

Declarations

Ethics approval and consent to participate

Our access to the MIMIC-III database was approved after completion of the CITI program course named “Human Research-Data or Specimens Only Research” (Record ID: 31532119). The project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and informed consent was waived due to the purely observational nature of the study. This study was approved by the ethics committee of Peking University Shenzhen Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available in the PhysioNet repository (https://physionet.org/content/mimiciii/1.4/).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Weixing Zhang and Youzhong An designed experiments; Jingying Chen, Weijia Li and Yiming Zhang extracted the data; Wencheng He, Lei Huang and Hua Luo performed the analysis. Wencheng He wrote the manuscript. All authors read and approved the final manuscript.

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Figures

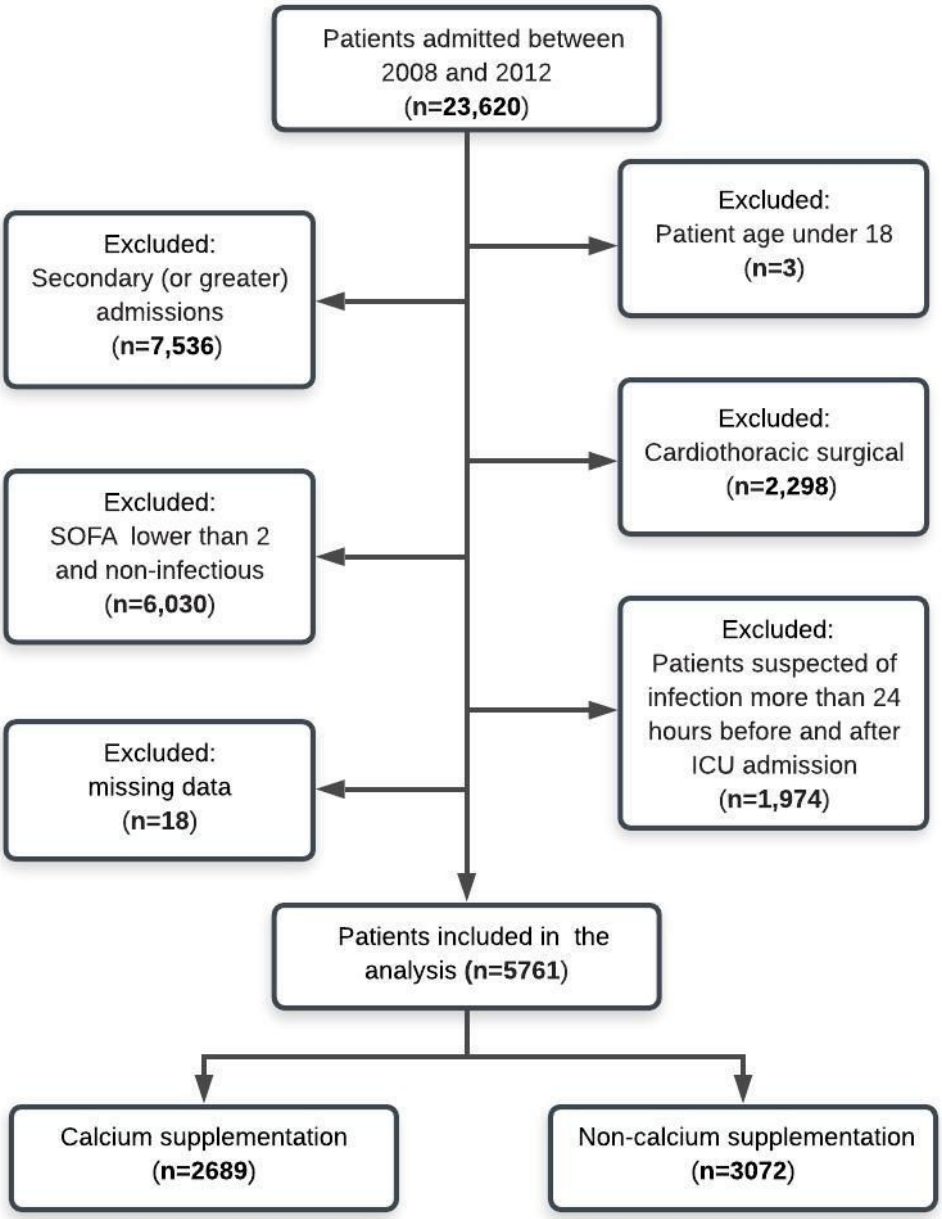

Figure 1

Illustration of exclusion and inclusion criteria as utilized to select the final cohort of 5761 patients

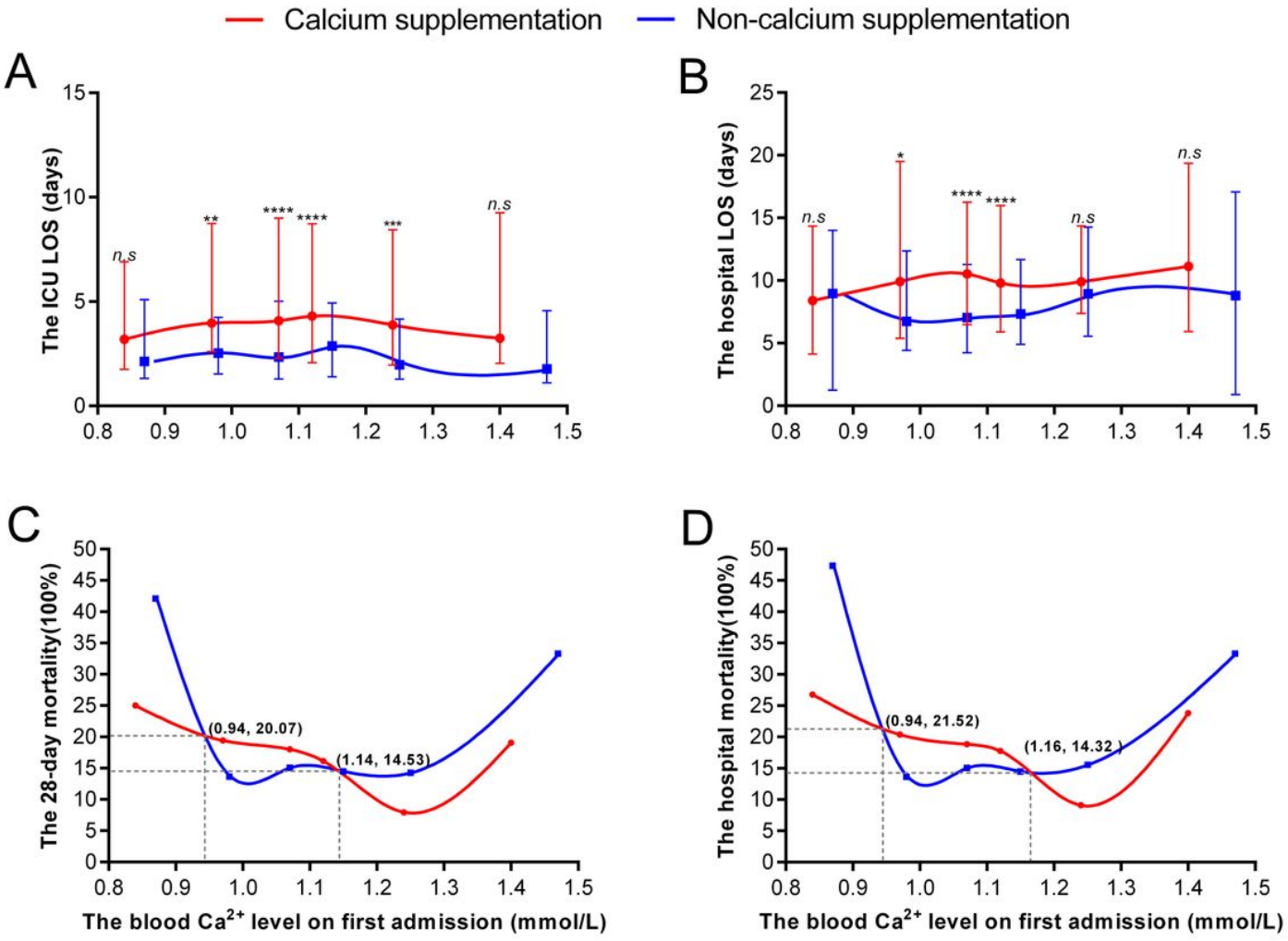

Figure 2

LOS and mortality in septic patients with or without calcium supplementation stratified by iCa on first-day ICU admission. The LOS in the ICU (A) and hospital (B) in the calcium supplement group were higher than that in the non-calcium supplement group. The data for each intervals are expressed as the median with interquartile range and were connected by using Lowess smoothing technique (Mann-Whitney U test, *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001, n.s. not significant); a higher 28-day (C) and hospital (D) mortality were found in the calcium supplement group when the iCa within 0.94~1.16 mmol/L, while a lower mortality of 28-day(C) and hospital(D) mortality were found in the calcium supplement group when the iCa was < 0.94 or >1.16. The data for each intervals were are expressed as percentage and connected by using Lowess smoothing technique.

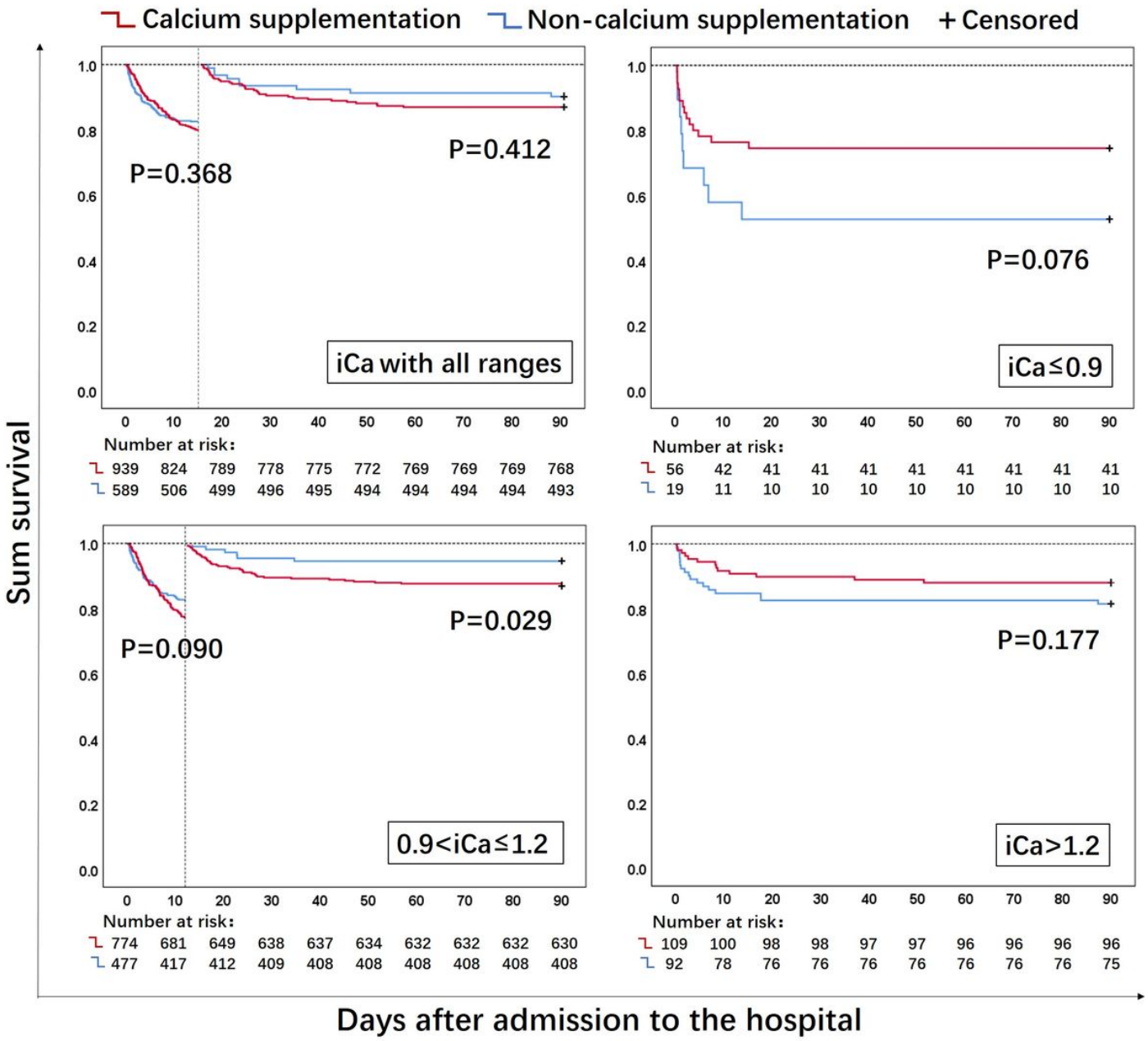

Figure 3

Landmark survival analysis of the difference in 90 mortality between the calcium supplement and non-calcium supplement septic patients stratified by iCa on first ICU admission

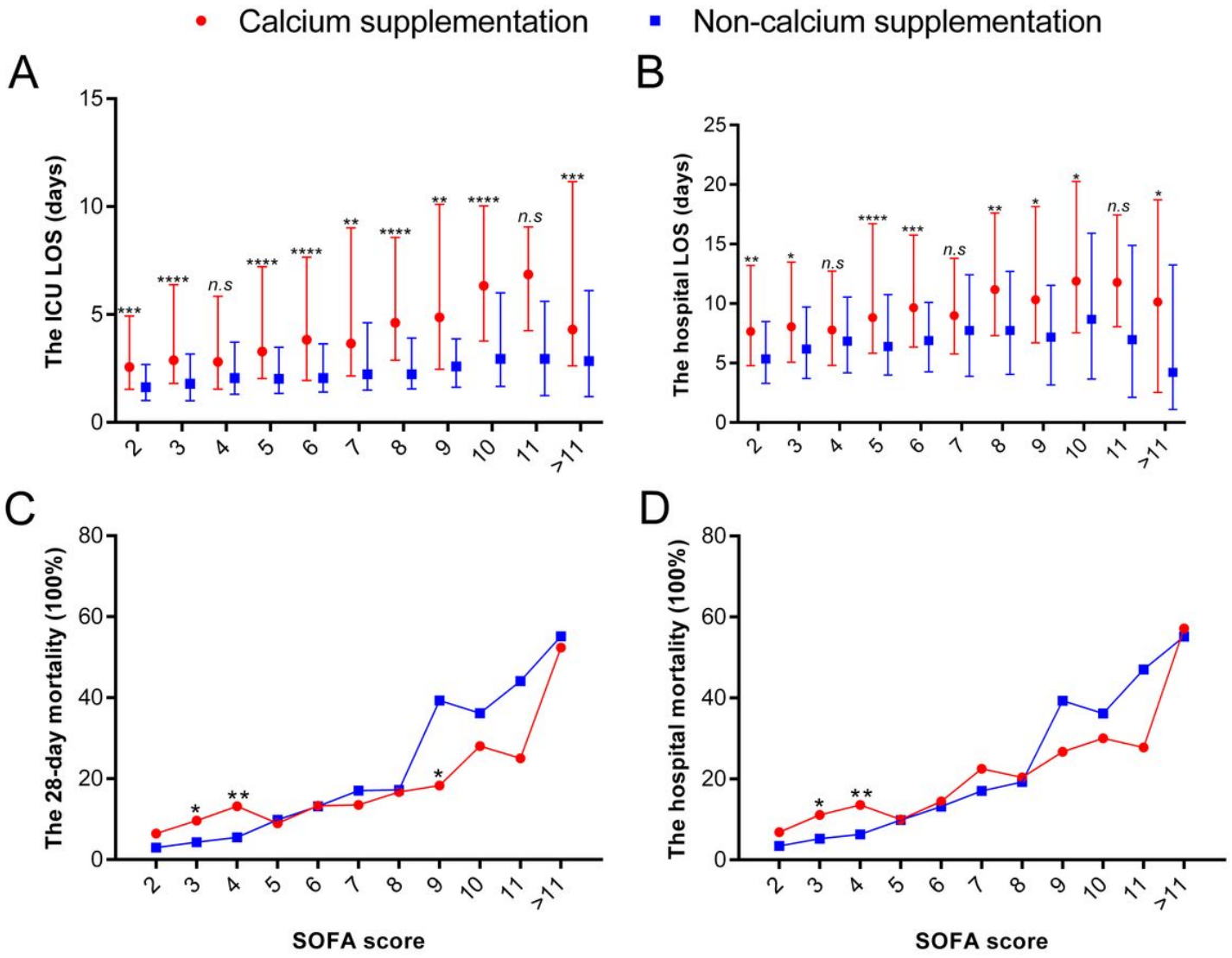

Figure 4

The LOS and mortality in septic patients with or without calcium supplementation stratified by the SOFA score. The LOS in the ICU (A) and hospital (B) in the calcium supplement group was higher than that in the non-calcium supplement group; the data for each intervals are expressed as the median with interquartile range (Mann-Whitney U test, *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001, n.s. not significant); a higher 28-day (C) and hospital (D) mortality was found in the calcium supplement group when the patient's SOFA score was >8, while a lower 28-day (C) and hospital (D) mortality was found in the calcium supplement group when the patient's SOFA score was <5, The data for each intervals were are expressed as percentage (Chi square test, *p<0.05; **p<0.01).

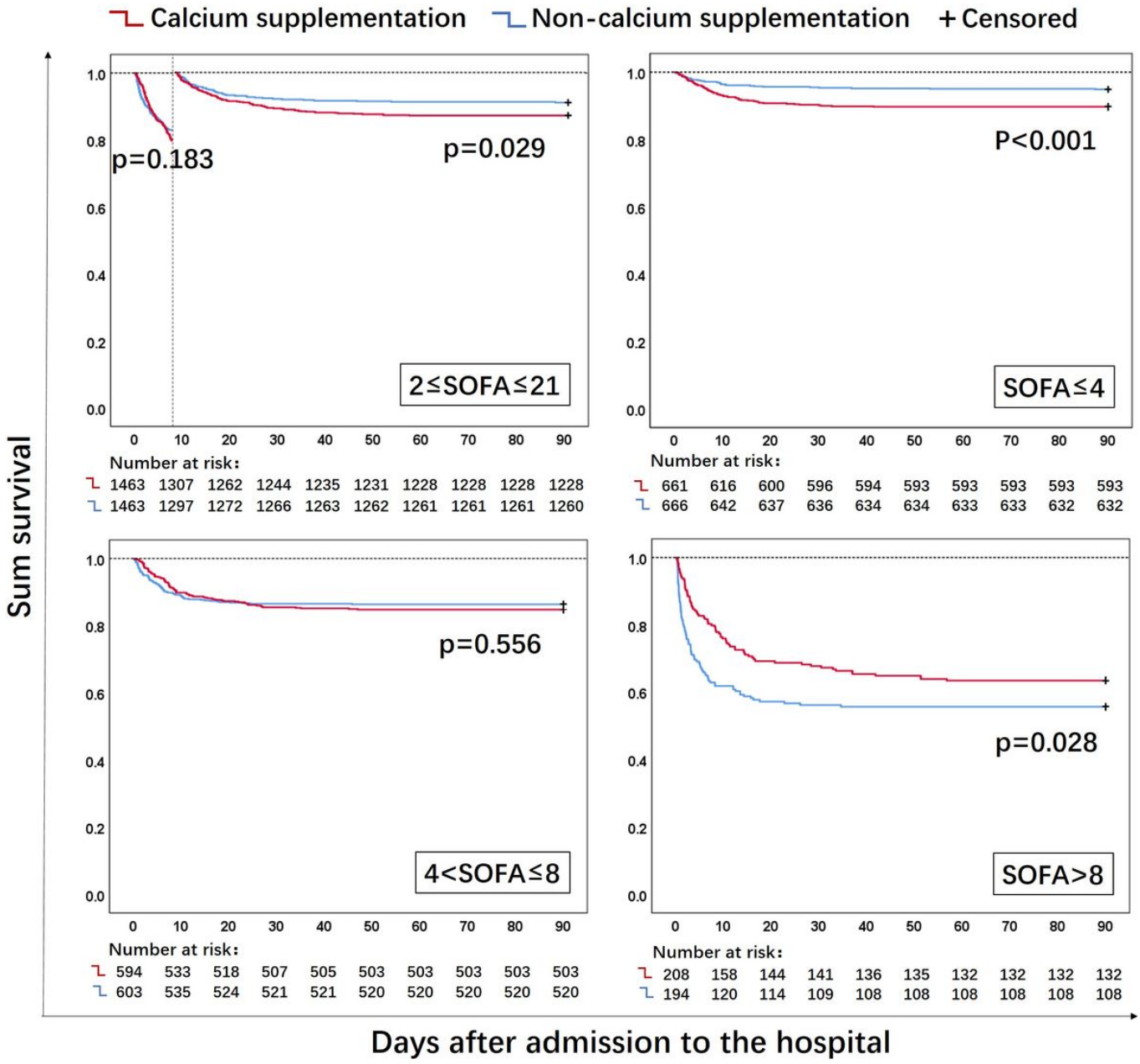

Figure 5

Landmark survival analysis of the difference in 90-day mortality between calcium supplement and non-calcium supplement septic patients stratified by the SOFA score