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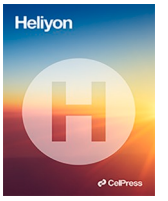

Research article

Association between serum calcium levels and in-hospital mortality in sepsis: A retrospective cohort study

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ABSTRACT

Background: This study examines serum calcium levels and in-hospital mortality in patients with sepsis, a subject with contradictory findings in the existing literature.
Methods: This retrospective cohort study utilized data from the MIMIC-IV database, focusing on adult patients diagnosed with sepsis between 2008 and 2019. The serum calcium levels were taken as the highest value within the first 24 h of Intensive Care Unit (ICU) admission. We performed Cox proportional hazards regression analyses in multivariable-adjusted models to investigate the association between serum calcium levels and in-hospital mortality. Restricted cubic spline functions were used to assess the nonlinear relationship, and threshold effect analysis was conducted to identify potential inflection points.
Results: A total of 18,546 patients with sepsis were included in the study, and an in-hospital mortality rate of 16.9 % (3,126 out of 18,546) was obtained. Furthermore, a U-shaped relationship was observed between serum calcium concentrations and in-hospital mortality, with the lowest point at approximately 8.23 mg/dL. Hazard ratios were calculated as 0.75 (95 % CI: 0.67–0.85, $P < 0.001$) on the left side and 1.10 (95 % CI: 1.04–1.16, $P < 0.001$) on the right side of the inflection point. Sensitivity analyses corroborated these results.
Conclusion: The research identified a U-shaped correlation between serum calcium concentrations and in-hospital mortality rates among patients with sepsis, underscoring the importance of serum calcium monitoring in this patient population upon hospital admission.

1. Introduction

Sepsis, which accounts for nearly 20 % of global annual deaths [1], arises from an anomalous response of the host's immune, leading to systemic inflammatory response syndrome (SIRS) [2]. This intricate pathophysiological cascade involves the spread of infectious agents, the release of inflammatory mediators, and increased microvascular permeability, potentially precipitating multi-organ dysfunction [3]. The dysregulation in calcium homeostasis during sepsis stems from an imbalance in calcium absorption and heightened discharge caused by inflammatory cytokines [4].

Serum calcium is crucial to vital physiological processes such as cell membrane stability, nerve conduction, muscle contraction, and coagulation [5,6]. Serum calcium exists in three forms: protein bound, complexed with anions, and free ionized calcium [7]. Ionized calcium constitutes the largest proportion and is the biologically active form [8]. However, measuring ionized calcium is both

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challenging and costly, which is why total calcium remains the most commonly used test in clinical practice [9]. Additionally, serum calcium can be used to estimate ionized calcium levels [10]. The physiological roles of serum calcium and ionized calcium are consistent in conditions such as bleeding and coagulation [11] and hyperparathyroidism [12]. Total calcium, therefore, remains the most commonly used test in clinical practice. Throughout the continuum of sepsis progression, the perturbation in serum calcium homeostasis intricately correlates with disease severity, manifesting both potential protective or deleterious effects [13]. Ambiguity exists regarding the association between serum calcium and in-hospital mortality among patients with sepsis. While certain studies assert a robust association between hypocalcemia/hypercalcemia and mortality [14–17], others posit that in-hospital mortality among patients with sepsis remains unrelated to serum calcium [18,19]. Consequently, further studies are needed to elucidate the precise mechanism and clinical translatability.

This study assesses the relationship between sepsis-related in-hospital mortality and calcium, concurrently evaluating the predictive efficacy of calcium concentration on sepsis progression. The study provides insights into sepsis pathogenesis, refines early diagnostic paradigms, strengthens clinical prognostication, and identifies novel avenues for pertinent clinical practices.

2. Participants and methods

2.1. MIMIC-IV database

In this study, we utilized data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, which is a large, freely-available database comprising de-identified health-related data from patients admitted to intensive care unit (ICU) at the Beth Israel Deaconess Medical Center between 2008 and 2019. This database contains records of more than 70,000 patients. The database is accessible to individuals who have passed the Collaborative Institutional Training Initiative exam, as indicated by Certification number 12432638, awarded to Hui Wang. Because of the retrospective nature of our research and the use of publicly accessible data, there was no need to obtain informed consent. The methodologies and reporting of our findings aligned with the principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

2.2. Study population

We sourced data from the MIMIC-IV database, encompassing patient admissions to the ICU between 2008 and 2019. Adult experiencing their first ICU admission, totaling 50,920 out of 73,181 individuals, were initially included in the study. Exclusion criteria were absence of sepsis (28,287 patients), lack of serum calcium data (2,193), and missing covariates including positive culture (1,224), anion gap (13), creatinine (2), heart rate (21), hemoglobin (22), mean arterial pressure (MAP) (21), platelets (20), respiratory rate (30), temperature (671), saturation of peripheral oxygen (SpO_2) (27), and white blood cell (WBC) count (19). Following these exclusions, the final cohort comprised 18,546 patients (Fig. 1). Data extraction included survival information from the 'patients' table and hospital stay durations from the 'admissions' table of the MIMIC-IV database [21].

2.3. Variables

Baseline serum calcium was measured as a continuous variable, defined by the highest recorded level within the initial 24 h post-ICU admission. Normal adult serum calcium levels typically range from 8.8 to 10.4 mg/dL. The primary outcome measure was in-hospital mortality after ICU admission. Sepsis diagnoses followed the criteria set by the Third International Consensus Definitions [22]. In constructing the fully-adjusted model, variables identified as potential confounders through literature review and clinical

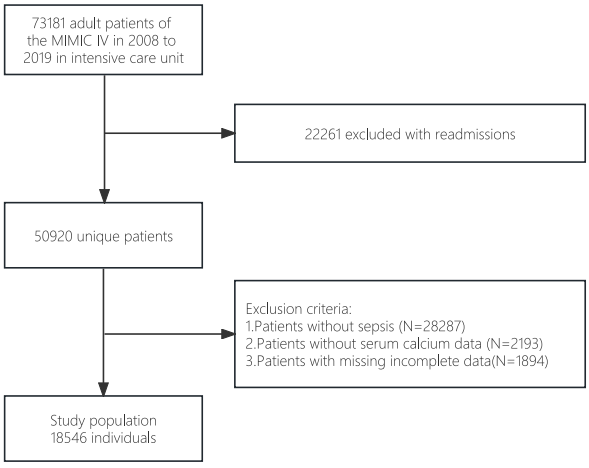

Fig. 1. Flow diagram of the screening and enrollment of study participants.

evaluation were included. Continuous variables incorporated into the model comprised age, heart rate, MAP, respiratory rate, temperature, SpO_2, hemoglobin concentration, platelet count, WBC count, anion gap, creatinine level, and the first 24-h scores from both the Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA). Categorical variables encompassed gender and the presence of clinical conditions and interventions such as myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, cancer, severe liver disease, presence of positive culture, application of vasopressors, renal replacement therapy (RRT), and mechanical ventilation. The clinical conditions were determined using International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes. ICD-10 was implemented in October 2015 in the United States. For variables recorded several times in the initial 24 h, we chose the mean heart rate, MAP, respiratory rate, temperature, SpO_2, the lowest levels of hemoglobin and platelets, the highest count of WBC, the highest creatinine, and anion gap.

2.4. Statistical analysis

Categorical variables were presented as either frequencies or percentages. To assess the differences between various serum calcium groups (categorized into quartiles), chi-square tests were used for categorical variables. For continuous variables, depending on their distribution, either parametric methods (in the case of normal distribution) or Kruskal-Wallis H tests (for skewed distributions) were used. The analysis used Cox proportional hazard models in a three-step approach. Initially, two types of models were employed: unadjusted models and multivariate-adjusted models. Model I: This model included two primary variables—age and gender. These basic demographic factors were used to establish a foundational understanding of the patient population. Model II: This model incorporated additional medical variables to provide a more comprehensive analysis. These variables included myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease (kidney disorders), cancer (various forms of aggressive cancer), and severe liver disease. Model III: Model II variables plus physiological and lab measurements including heart rate, MAP, respiratory rate, temperature, SpO_2, hemoglobin levels, platelets count, WBC count, anion gap, creatinine levels, SAPA II, SOFA scores, vasopressor use, and positive culture. Model IV: Model III variables plus RRT and mechanical ventilation. The second step examined the potential non-linear relationship between serum calcium levels and in-hospital mortality, using a Cox regression model with cubic spline functions to plot the curve. In instances of nonlinearity, a two-piecewise model was formulated around a recursively determined inflection point. Finally, sensitivity analyses were conducted to assess the influence of serum calcium levels on in-hospital mortality.

All statistical analyses were performed using R version 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.9. The threshold for statistical significance was set at $P < 0.05$.

Table 1
Baseline characteristics of patients.

Variables	Total	Q1 (≤7.9 mg/dL)	Q2 (8.0–8.4 mg/dL)	Q3 (8.5–8.9 mg/dL)	Q4 (≥9.0 mg/dL)	*P*-value
No.	18,546	4252	4918	4700	4676	
Female	8085 (43.6)	1820 (42.8)	2052 (41.7)	2040 (43.4)	2173 (46.5)	<0.001
Age, y	66.4 ± 16.8	64.4 ± 16.9	66.4 ± 16.7	67.3 ± 16.9	67.4 ± 16.7	<0.001
Heart rate, b/min	87.4 ± 16.5	90.4 ± 16.6	87.4 ± 16.2	86.0 ± 16.4	86.1 ± 16.6	<0.001
MAP, mmHg	76.9 ± 10.5	74.7 ± 9.9	76.2 ± 9.9	78.0 ± 10.6	78.6 ± 11.3	<0.001
Respiratory rate, b/min	19.9 ± 4.1	20.3 ± 4.4	19.8 ± 4.1	19.7 ± 4.0	19.9 ± 4.0	<0.001
Temperature, °C	36.9 ± 0.6	36.9 ± 0.7	36.9 ± 0.6	36.9 ± 0.6	36.8 ± 0.6	<0.001
SpO_2, %	96.8 ± 2.5	96.8 ± 2.7	96.9 ± 2.2	96.8 ± 2.2	96.7 ± 2.6	0.0039
Hemoglobin, g/L	10.0 ± 2.2	9.5 ± 2.0	9.9 ± 2.1	10.2 ± 2.2	10.4 ± 2.4	<0.001
Platelets, $*10^3$/μL	165.0 (111.0, 231.0)	142.5 (95.0, 205.2)	163.0 (112.2, 223.0)	174.0 (123.0, 239.0)	180.0 (120.0, 246.0)	<0.001
WBC, $*10^3$/μL	13.6 (9.7, 18.6)	13.6 (9.2, 19.4)	13.9 (9.7, 18.8)	13.4 (9.8, 18.2)	13.5 (9.8, 18.2)	**0.143**
Anion gap, mmol/L	17.2 ± 5.3	16.5 ± 5.4	16.4 ± 4.9	17.0 ± 4.7	18.8 ± 6.0	<0.001
Creatinine, mg/dL	1.2 (0.8, 1.9)	1.1 (0.8, 1.9)	1.1 (0.8, 1.7)	1.2 (0.8, 1.8)	1.3 (0.9, 2.1)	<0.001
Myocardial infarct	2997 (16.2)	478 (13.7)	544 (15.1)	521 (16.6)	761 (17.2)	<0.001
Congestive heart failure	5237 (28.2)	908 (21.4)	1321 (26.9)	1493 (31.8)	1515 (32.4)	<0.001
Cerebrovascular disease	2674 (14.4)	432 (10.2)	611 (12.4)	746 (15.9)	885 (18.9)	<0.001
Chronic pulmonary disease	4808 (25.9)	1013 (23.8)	1261 (25.6)	1247 (26.5)	1287 (27.5)	<0.001
Renal disease	4096 (22.1)	732 (17.2)	994 (20.2)	1101 (23.4)	1269 (27.1)	<0.001
Severe liver disease	1450 (7.8)	366 (8.6)	335 (6.8)	324 (6.9)	425 (9.1)	<0.001
Malignant cancer	2757 (14.9)	706 (16.6)	712 (14.5)	653 (13.9)	686 (14.7)	0.007
SAPA II	39.8 ± 14.6	40.5 ± 15.1	39.0 ± 14.3	38.9 ± 14.3	41.1 ± 14.8	<0.001
SOFA	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	<0.001
RRT	382 (2.1)	67 (1.6)	77 (1.6)	86 (1.8)	152 (3.3)	<0.001
Machanical ventilation	25 (0.1)	0 (0)	7 (0.1)	8 (0.2)	10 (0.2)	0.039
Vasopressor	2050 (11.1)	617 (14.5)	488 (9.9)	414 (8.8)	531 (11.4)	<0.001
Positive culture	2815 (15.2)	689 (16.2)	728 (14.8)	687 (14.6)	711 (15.2)	**0.16**
Hospital stay(day)	8.4 (5.0, 14.9)	8.2 (4.9, 15.3)	8.3 (5.1, 14.7)	8.4 (5.0, 14.7)	8.6 (4.8, 15.2)	**0.968**
In-hospital mortality	3126 (16.9)	755 (17.8)	703 (14.3)	725 (15.4)	943 (20.2)	<0.001

Notes: data presented are mean ± SD, median (IQR), or N (%).
Abbreviations: Q1-Q4, quantiles based on serum calcium; MAP, mean arterial pressure; WBC, white blood cell; SAPS II, Simplified Acute Physiology Score ll; SOFA, Sequential Organ Failure; RRT, renal replacement therapy; SD, standard deviation; IQR, interquartile range.

3. Results

3.1. Baseline characteristics of selected participants

A total of 18,546 patients were incorporated into the final data set, as depicted in the flow chart (Fig. 1). Baseline characteristics categorized by serum calcium quartiles are presented in Table 1. The age of the cohort was 66.4 ± 16.8 years, 56.4 %. of the population being men. Statistical analyses revealed significant differences between the different serum calcium groups ($P < 0.05$) in several parameters, except WBC count, duration of hospitalization, presence of positive culture, and vasopressor usage. Participants in the highest serum calcium quartile (Q4, ≥9.0 mg/dL) demonstrated elevated levels of age, MAP, hemoglobin, platelet count, anion gap, and creatinine, along with increased SAPA II. This group also demonstrated a higher incidence of myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, severe liver disease, utilization of RRT, mechanical ventilation, and in-hospital mortality. The opposite patterns were observed in heart rate, respiratory rate, temperature, and SpO_2.

3.2. Univariate analysis

The outcomes of univariate analyses are tabulated in Table 2. Using the univariate Cox proportional hazard model, it was determined that RRT, mechanical ventilation, and positive culture presence exhibited no significant correlation with in-hospital mortality. Conversely, MAP, body temperature, SpO_2, hemoglobin levels, and platelet count demonstrated a negative correlation with in-hospital mortality. In contrast, the univariate analysis indicated that elevated serum calcium levels, female gender, increased age, heightened heart rate, elevated respiratory rate, higher WBC count, increased anion gap, elevated creatinine levels, and the presence of conditions such as myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, cancer, and severe liver disease were positively associated with in-hospital mortality. Additionally, higher scores on SAPA II, SOFA, and the use of vasopressors also correlated positively with in-hospital mortality.

3.3. Unadjusted and adjusted cox proportional hazard model

We adjusted four models to analyze the independent effects of serum calcium on in-hospital mortality (multivariate Cox proportional hazard model). The effect sizes (Hazard ratio [HR]) and 95 % confidence intervals (CIs) are listed in Table 3. The multivariate Cox regression analysis revealed that when serum calcium level was treated as a continuous variable, its association with mortality was not statistically significant. However, when considered as a categorical variable, a second group of serum calcium levels (8.0–8.4 mg/

Table 2
Univariate analysis for in-hospital mortality.

Covariate	HR(95%CI)	*P*
Calcium, mg/dL	1.08 (1.04,1.11)	<0.001
Gender:Female vs male	1.10 (1.03,1.19)	0.006
Age (y)	1.02 (1.02,1.03)	<0.001
Heart rate, b/min	1.01 (1.01,1.01)	<0.001
MAP, mmHg	0.97 (0.97,0.97)	<0.001
Respiratory rate, b/min	1.08 (1.08,1.09)	<0.001
Temperature, °C	0.58 (0.55,0.60)	<0.001
SpO_2, %	0.88 (0.87,0.89)	<0.001
Hemoglobin, g/L	0.96 (0.95,0.98)	<0.001
Platelets, $*10^3/\mu L$	1.00 (1.00,1.00)	<0.001
WBC, $*10^3/\mu L$	1.00 (1.00,1.00)	<0.001
Aniongap, mmol/L	1.08 (1.07,1.08)	<0.001
Creatinine, mg/dL	1.08 (1.07,1.10)	<0.001
Myocardial infarct	1.34 (1.23,1.46)	<0.001
Congestive heart failure	1.28 (1.19,1.38)	<0.001
Cerebrovascular disease	1.19 (1.09,1.30)	<0.001
Chronic pulmonary disease	1.10 (1.01,1.19)	0.02
Renal disease	1.23 (1.14,1.34)	<0.001
Malignant cancer	1.39 (1.28,1.51)	<0.001
Severe liver disease	1.46 (1.31,1.61)	<0.001
SAPA II	1.05 (1.04,1.05)	<0.001
SOFA	1.12 (1.11,1.14)	<0.001
RRT	1.15 (0.93,1.43)	0.199
Machanical ventilation	0.55 (0.18,1.72)	0.308
Vasopressor	3.77 (3.51,4.06)	<0.001
Positive culture	1.09 (0.99,1.19)	0.078

Note: data presented are HRs and 95 % CIs.
Abbreviations: MAP, mean arterial pressure; WBC, white blood cell; SAPSII, Simplified Acute Physiology Score ll; SOFA, Sequential Organ Failure; RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval.

dL) was used as a baseline reference. Relative to this group, both the lowest (Q1, ≤7.9 mg/dL) and highest (Q4, ≥9.0 mg/dL) quartiles of serum calcium level were observed to be significantly associated with increased in-hospital mortality (crude HR: 1.21, 95 % CI: 1.09–1.34, $P < 0.001$ for Q1; crude HR: 1.36, 95 % CI: 1.24–1.50, $P < 0.001$ for Q4). This association of serum calcium levels with mortality remained consistently significant across all analyzed models. In Model IV, after further adjusting all confounders, the significant associations of Q1 and Q4 with increased in-hospital mortality remained (adjusted HR for Q1: 1.19, 95 % CI: 1.07–1.32, $P < 0.001$; adjusted HR for Q4: 1.22, 95 % CI 1.10–1.35, $P < 0.001$). The *P*-value for the trend of serum calcium level with categorical variables in the fully adjusted model was 0.137, consistent with the results obtained when serum calcium level was treated as a continuous variable. Additionally, we observed that the trend of the effect size in different serum calcium groups was non-equidistant. Fig. 2 presents the nonlinear relationship between serum calcium level and in-hospital mortality. The smooth curve from the Cox proportional hazards regression model with cubic spline functions demonstrated this nonlinear association after adjustments for potential confounders. Using the two-piecewise Cox proportional hazard model (Table 4), the inflection point was calculated to be 8.23 mg/dL. On the left side of this inflection point, the effect size and 95 % CI were 0.75 (95 % CI: 0.67–0.85), while on the right side, they were 1.10 (95 % CI: 1.04–1.16), highlighting differing associations with mortality across varying serum calcium levels.

3.4. Sensitivity analysis

Patients with serum calcium values exceeding three standard deviations were excluded. As a result, 18,364 patients were included in this study cohort. Notably, the relationship between serum calcium levels and in-hospital mortality persisted. Relative to the reference group (Q2, 8.0–8.4 mg/dL), the adjusted HR for in-hospital mortality in the quartiles Q1 (≤7.9 mg/dL), Q3 (8.5–8.9 mg/dL), and Q4 (≥9.0 mg/dL) were 1.18 (95 % CI: 1.07–1.31, $P = 0.002$), 1.15 (95 % CI: 1.03–1.27, $P = 0.01$), and 1.20 (95 % CI: 1.09–1.33, $P < 0.001$), respectively (Supplementary Table S1). Furthermore, the lowest serum calcium values recorded on the first day of ICU admission from the MIMIC-IV dataset for patients with sepsis were used to corroborate the association between serum calcium levels and in-hospital mortality, with an effect value of 1.16 (HR: 1.16, 95 % CI: 1.01–1.32, $P = 0.034$) (>9.0 mg/dL vs. 8.0–8.4 mg/dL) (Supplementary Table S2).

4. Discussion

The analysis revealed a U-shaped relationship between serum calcium levels and in-hospital mortality, characterized by differing effect sizes on the left (HR: 0.75, 95 % CI: 0.67–0.85) and right (HR: 1.10, 95 % CI: 1.04–1.16) sides of the inflection point. This finding persisted even after adjusting for a range of covariates, indicating a complex and nonlinear association. Consistent with previous research, our findings indicate that the lowest mortality rates among patients with sepsis are associated with serum calcium levels that are slightly below the normal range [23]. Previous studies have reported an association between septicemia and low serum calcium levels, and have cautioned against the supplementation of calcium in such cases, as it is often unhelpful or potentially harmful [14,15,24]. This observation suggests a possible trend where serum calcium levels in patients with septicemia might normalize gradually as they recover.

Yan et al. posited a U-shaped curve in the relationship between serum calcium levels and 28-day mortality in patients with sepsis, based on an analysis of 3,016 participants [16]. This conclusion aligns with our findings. However, there are several studies with divergent results. Wang et al., for instance, reported no independent association between serum calcium levels and hospital mortality in patients with sepsis, although they, like us, observed a U-shaped curve in the relationship between serum calcium levels and in-hospital mortality [19]. Additionally, Gallardo et al. identified a correlation between mortality, sepsis, and hypoalbuminemia but

Table 3
Association between serum calcium levels and in-hospital mortality.

	Nonadjusted	*P*-value	Model I	*P*-value	Model II	*P*-value	Model III	*P*-value	Model IV	*P*-value
Calcium, mg/dL	1.08(1.04-1.11)	<0.001	1.07(1.04-1.11)	<0.001	1.05 (1.02-1.09)	0.005	1.04(1.01-1.07)	0.011	1.02(0.99-1.06)	0.205
Quantiles										
Q1(≤7.9)	1.21(1.09-1.34)	<0.001	1.27(1.14-1.41)	<0.001	1.26(1.14-1.40)	<0.001	1.14(1.02-1.26)	0.016	1.19(1.07-1.32)	0.001
Q2(8.0–8.4)	Ref		Ref		Ref		Ref		Ref	
Q3(8.5–8.9)	1.08(0.98-1.20)	0.135	1.06 0.95–1.17)	0.288	1.04 0.94–1.16)	0.442	1.12(1.01-1.24)	0.031	1.15(1.03-1.28)	0.009
Q4(≥9.0)	1.36(1.24-1.50)	<0.001	1.34(1.22-1.48)	<0.001	1.28(1.16-1.41)	<0.001	1.26(1.14-1.39)	<0.001	1.22 (1.10-1.35)	<0.001
P for trend		0.002		0.058		0.347		0.005		0.137

Notes: data presented are HRs and 95 % CIs.
Model I was adjusted for age and gender; model II was adjusted for model I + myocardial infarct, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, malignant cancer, severe liver disease; model III was adjusted for model II + heart rate, MAP, respiratory rate, temperature, SpO_2, hemoglobin, platelets, WBC, aniongap, creatinine, SAPA II, SOFA, vasopressor, positive culture; model IV was adjusted for model III + RRT, machanical ventilation.
Abbreviations: MAP, mean arterial pressure; WBC, white blood cell; SAPS II, Simplified Acute Physiology Score ll; SOFA, Sequential Organ Failure; RRT, renal replacement therapy; Cl, confidence interval; HR, hazard ratio; Q, quantile.

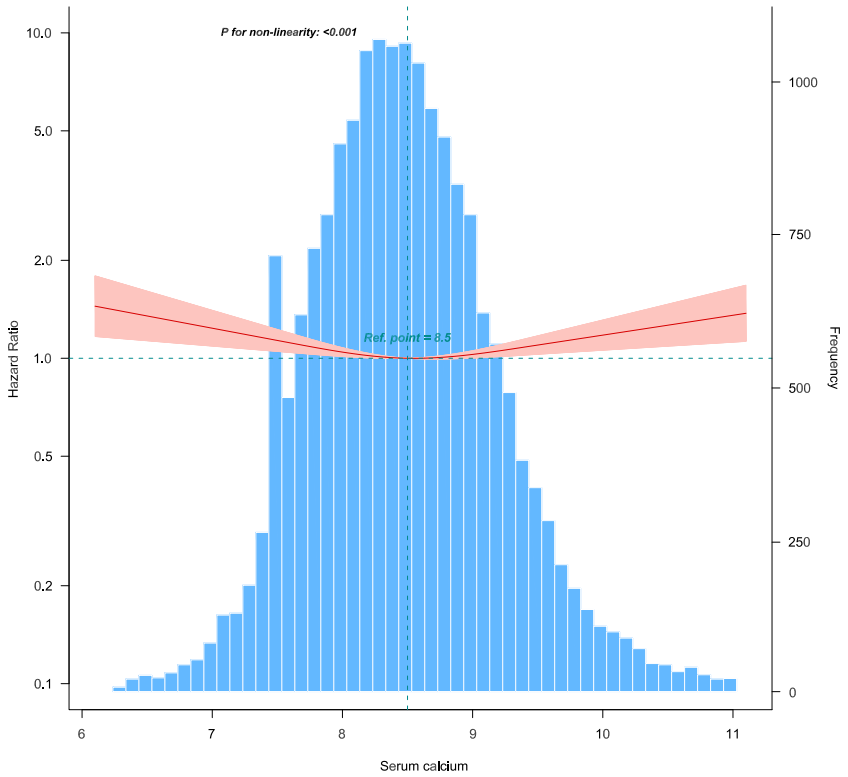

Fig. 2. The nonlinear relationship between serum calcium and in-hospital mortality of sepsis in Intensive Care Unit (ICU). The risk ratio (solid line) and 95 % confidence interval (shaded area) were calculated using the Cox proportional hazards model, with adjustments for covariates. The frequency bars illustrate the distribution of patients based on their serum calcium levels. Notes: adjusted for age, sex, myocardial infarct, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, malignant cancer, severe liver disease, heart rate, mean arterial pressure (MAP), respiratory rate, temperature, SpO_2, hemoglobin, platelets, white blood cells (WBC), anion gap, creatinine, SAPA II, SOFA, vasopressor, renal replacement therapy (RRT), machanical ventilation, positive culture. Abbreviations: SAPS II, Simplified Acute Physiology Score ll; SOFA, Sequential Organ Failure.

Table 4
Threshold effect analysis of serum calcium levels and the in-hospital mortality of sepsis using Cox regression models.

	HR(95%CI)	*P*-value
Turning point (mg/dL)	8.23	
Calcium <8.23	0.75 (0.67,0.85)	<0.001
Calcium ≥8.23	1.10 (1.04,1.16)	<0.001
Likelihood Ratio test		<0.001

Notes: Data presented are HRs and 95 % CIs.
Adjusted for age, sex, myocardial infarct, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, malignant cancer, severe liver disease, heart rate, MAP, respiratory rate, temperature, SpO_2, hemoglobin, platelets, WBC, anion gap, creatinine, SAPA II, SOFA, vasopressor, RRT, machanical ventilation, positive culture.
Abbreviations: MAP, mean arterial pressure; WBC, white blood cell; SAPS II, Simplified Acute Physiology Score ll; SOFA, Sequential Organ Failure; RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval.

not with corrected serum calcium levels [18]. Upon examining the conflicting study of Gallardo, we speculate that the differences could be attributed to several factors:(1) The target population in their studies comprised 44 critically ill patients, which is a considerably smaller and more specific group compared to ours. (2) Their study focused corrected serum calcium levels rather than total serum calcium levels. These variations in study design and focus may also account for the conflicting findings.

Calcium ions play a pivotal role in cellular signaling, particularly within immune cells. The modulation of this signaling process during sepsis can significantly impact inflammatory and immune responses [25–28]. Vascular dysfunction, a common complication in sepsis, may be linked to changes in serum calcium levels, as evidenced by similarities with sepsis-related coagulation abnormalities

observed in COVID-19 [29,30]. Furthermore, the critical role calcium plays in cardiac function and coagulation processes suggests that abnormalities in serum calcium levels can impair cardiac function and disrupt coagulation mechanisms in sepsis [31]. This conclusion is supported by findings indicating a correlation between hemostatic activation- and inflammation-related biomarkers and changes in coagulation parameters, indicating a potential association with calcium level fluctuations. Additionally, the frequent observation of hypocalcemia in patients with sepsis and its association with increased mortality risk underscores the importance of calcium in the severity and treatment outcomes of sepsis. These insights highlight the need for further research to elucidate the specific roles and mechanisms of serum calcium levels in the pathogenesis of sepsis.

Our findings offer critical insights that are expected to significantly influence future research focused on developing models for diagnosing and predicting in-hospital mortality rates among patients with sepsis. This study assessed the correlation between serum calcium concentrations and mortality rates in sepsis, laying the foundation for future models and potentially enhancing their precision and effectiveness. Additionally, this study goes beyond merely identifying the nonlinearity in the correlation between serum calcium concentrations and in-hospital mortality rates. It enriched our understanding of this intricate association. Although observational studies are inherently prone to confounding, our study addressed this concern through meticulous statistical adjustments. This methodological rigor significantly minimized the impact of potential confounders and reinforced the credibility of our results. Our study addressed serum calcium as both a continuous and categorical variable, a strategy that mitigated the risk of arbitrary data analysis outcomes and solidified the robustness of our findings. By conducting an extensive analysis of potential effect modifiers, our study not only used the data to its fullest extent but also ensured that our conclusions were stable and consistent across different patients. This research marks a pioneering effort to analyze the correlation between serum calcium concentrations and in-hospital mortality rates using the MIMIC-IV dataset. Collectively, these strengths underscore the study's substantial contribution to enhancing our understanding of the prognostic role of serum calcium in hospitalized patients, particularly those with sepsis. The comprehensive approach and methodological robustness of this study ensure its relevance and applicability in clinical and research settings.

The present study, while contributing valuable insights, is subject to several limitations. Firstly, our research focused exclusively on patients with sepsis. Therefore, the generalizability and extrapolation of our findings are constrained. Therefore, patients without sepsis, those lacking serum calcium data, and those with missing covariates were excluded from our analysis, limiting the applicability of our results to these populations. Moreover, given the inherent risk of bias associated with retrospective cohort studies, we adjusted for potential confounding factors. However, the possibility of residual bias could not be eliminated. Establishing a definitive causal relationship and understanding the underlying mechanisms linking calcium derangements with outcomes in septic patients remains challenging. Thus, this study, by its nature, could not conclusively determine causation. Furthermore, the fact that our study was conducted within a single institution introduces the potential for selection bias, which may impact the representativeness of our study population and, consequently, the generalizability of our findings. Additionally, given the limitations of the data extraction process, we were unable to gather information on patients who were transferred to another hospital or discharged to their homes at the end of their life, which may have led to an underestimation of the true in-hospital mortality rate in our analysis. Finally, we focused on serum calcium levels in patients with sepsis, which is not a complete substitute for ionized calcium levels. These limitations underscore the need for a cautious interpretation of our results and suggest avenues for future research to further elucidate the intricate association between serum calcium concentrations and outcomes among patients with sepsis.

5. Conclusion

Our research elucidated a U-shaped correlation between serum calcium levels and in-hospital mortality in patients with sepsis. This finding underscores the clinical need for healthcare providers to diligently monitor serum calcium levels upon patient admission.

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Ethical considerations and informed consent

This database was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center, with the approval number (2001-P-001699/14) and the Massachusetts Institute of Technology, with the approval number (No. 0403000206). The data in this research are accessible through the MIMIC database. As a result, informed consent and ethical approval were waived.

Consent for publication

Not applicable.

Data availability statement

The data in this article is accessible from the MIMIC-IV database (https://mimic.physionet.org/). Additionally, the data obtained and analyzed in this study are available upon request from the corresponding author.

CRediT authorship contribution statement

Hui Wang: Writing – original draft, Investigation, Formal analysis, Data curation. **Hui Sun:** Visualization, Supervision, Project administration. **Jinping Sun:** Writing – review & editing, Validation, Software, Methodology, Conceptualization.

Declaration of competing interest

None.

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List Of Abbreviations

BUN	blood urea nitrogen
ICU	intensive care unit
MAP	mean arterial pressure
RRT	renal replacement therapy
SAPS II	Simplified Acute Physiology Score II
SIRS	systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SpO_2	saturation of peripheral oxygen
WBC	white blood cell

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34702.

References

[1] J.A. Kempker, G.S. Martin, A global accounting of sepsis, Lancet Lond. Engl. 395 (2020) 168–170.
[2] S. Shafik, S. Mallick, J. Fogel, et al., The utility of systemic inflammatory response syndrome (SIRS) for diagnosing sepsis in the immediate postpartum period, J. Infect. Public Health 12 (2019) 799–802.
[3] K.E. Rudd, S.C. Johnson, K.M. Agesa, et al., Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study, Lancet Lond. Engl. 395 (2020) 200–211.
[4] A. Sood, G. Singh, T.G. Singh, et al., Pathological role of the calcium-sensing receptor in sepsis-induced hypotensive shock: therapeutic possibilities and unanswered questions, Drug Dev. Res. 83 (2022) 1241–1245.
[5] A.L. Olicker, A.A. Fanaroff, J.M. Fanaroff, et al., Disorders of calcium, phosphorous, and magnesium in the newborn, in: G.I. Martin, W. Rosenfeld (Eds.), Common Probl. Newborn Nurs., Springer International Publishing, Cham, 2019, pp. 109–115.
[6] X. Xu, S.P. Balk, W.B. Isaacs, et al., Calcium signaling: an underlying link between cardiac disease and carcinogenesis, Cell Biosci. 8 (2018) 39.
[7] M. Peacock, Calcium metabolism in health and disease, Clin. J. Am. Soc. Nephrol. 5 (2010) S23–S30.
[8] G.S. Baird, Ionized calcium, Clin. Chim. Acta Int. J. Clin. Chem. 412 (2011) 696–701.
[9] C.M. Clase, G.L. Norman, M.L. Beecroft, et al., Albumin-corrected calcium and ionized calcium in stable haemodialysis patients, Nephrol. Dial. Transplant. 15 (2000) 1841–1846.
[10] W.-L. Hung, C.-F. Huang, M.-H. Tsait, et al., A new predictive equation for estimating serum ionized calcium levels in patients on chronic hemodialysis, Med. Sci. Monit. 29 (2023).
[11] A. Morotti, A. Charidimou, C.-L. Phuaht, et al., Association between serum calcium level and extent of bleeding in patients with intracerebral hemorrhage, JAMA Neurol. 73 (2016) 1285.
[12] L. Benson, S. Ljunghall, T. Grotht, et al., Optimal discrimination of mild hyperparathyroidism with total serum calcium, ionized calcium and parathyroid hormone measurements, ups, J. Med. Sci. 92 (1987) 147–176.
[13] E. Ghafouri, M. Bigdeli, A. Khalafiyan, et al., Unmasking the complex roles of hypocalcemia in cancer, COVID-19, and sepsis: engineered nanodelivery and diagnosis, Environ. Res. 238 (2023) 116979.
[14] M. Fei, P. Li, X. Tao, et al., [Influence of hypocalcemia on the prognosis of septic patients], Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 31 (2019) 418–421.
[15] H. Li, J. Chen, Y. Hu, et al., Clinical value of serum calcium in elderly patients with sepsis, Am. J. Emerg. Med. 52 (2022) 208–211.
[16] D. Yan, X. Xie, X. Fu, et al., U-SHAPED association between serum calcium levels and 28-DAY mortality in patients with sepsis: a retrospective analysis of the MIMIC-III database, Shock 60 (2023) 525–533.
[17] C. Thongprayoon, P. Hansrivijit, T. Petnak, et al., Hospital-acquired serum ionized calcium derangements and their associations with in-hospital mortality, Med. Basel Switz. 7 (2020) 70.
[18] J. Gallardo, P. Fardella, H. Pumarino, et al., [Plasma calcium levels in critical patients with and without sepsis], Rev. Med. Chil. 119 (1991) 262–266.
[19] B. Wang, Y. Gong, B. Ying, et al., Association of initial serum total calcium concentration with mortality in critical illness, BioMed Res. Int. 2018 (2018) 7648506.

[20] E. von Elm, D.G. Altman, M. Egger, et al., Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, BMJ 335 (2007) 806–808.
[21] A.E. Johnson, D.J. Stone, L.A. Celi, et al., The MIMIC Code Repository: enabling reproducibility in critical care research, J. Am. Med. Inform. Assoc. JAMIA 25 (2018) 32–39.
[22] M. Singer, C.S. Deutschman, C.W. Seymour, et al., The Third International Consensus Definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (2016) 801.
[23] Y. Mao, S. Zhu, Y. Geng, Association between serum calcium and in-hospital mortality in critical patients with multiple myeloma: a cohort study, Hematology 27 (2022) 795–801.
[24] R.D. Collage, G.M. Howell, X. Zhang, et al., Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase kinase signaling, Crit. Care Med. 41 (2013) e352–e360.
[25] G. Maiti, J. Frikeche, C.Y.M. Lam, et al., Matrix lumican endocytosed by immune cells controls receptor ligand trafficking to promote TLR4 and restrict TLR9 in sepsis, Proc. Natl. Acad. Sci. 118 (2021) e2100999118.
[26] G. Morris, M. Gevezova, V. Sarafian, et al., Redox regulation of the immune response, Cell, Mol. Immunol. 19 (2022) 1079–1101.
[27] F. Feng, P. Jiao, J. Wang, et al., Role of long noncoding RNAs in the regulation of cellular immune response and inflammatory diseases, Cells 11 (2022) 3642.
[28] W.H. Almalki, The sepsis induced defective aggravation of immune cells: a translational science underling chemico-biological interactions from altered bioenergetics and/or cellular metabolism to organ dysfunction, Mol. Cell. Biochem. 476 (2021) 2337–2344.
[29] X. Qi, H. Kong, W. Ding, et al., Abnormal coagulation function of patients with COVID-19 is significantly related to hypocalcemia and severe inflammation, Front. Med. 8 (2021) 638194.
[30] X. Zhou, D. Chen, L. Wang, et al., Low serum calcium: a new, important indicator of COVID-19 patients from mild/moderate to severe/critical, Biosci. Rep. 40 (2020). BSR20202690.
[31] Y.C. Liu, M.M. Yu, S.T. Shou, et al., Sepsis-Induced cardiomyopathy: mechanisms and treatments, Front. Immunol. 8 (2017) 1021.