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Original Research Article

ROLE OF SERUM IONIZED CALCIUM AS A PROGNOSTIC MARKER IN SEPSIS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Sepsis is a life-threatening syndrome with high mortality despite advances in critical care. Calcium plays a central role in cardiovascular, immune, and endothelial function. However, the utility of serum ionized calcium (iCa2+) as a prognostic marker — particularly when measured serially remains undercharacterised in the Indian context. The objective is to evaluate serum ionized calcium as a biomarker in sepsis; (2) To assess its correlation with disease severity using APACHE II and SOFA scores. **Materials and Methods:** A single-centre prospective observational study of 240 adult sepsis patients (Sepsis-3 criteria) admitted to the ICU and medical wards of a tertiary care hospital over 18 months. Serum iCa2+ was measured on Day 1, Day 4, and Day 7. Patients were stratified by calcium trend (increasing vs. decreasing). Primary outcomes were mortality and correlation with severity scores. **Result:** Mean age was 57.8 ± 14.6 years; 57.5% were male. Hypocalcaemia (iCa2+ < 1.15 mmol/L) was present in 43.7% at admission. Critically, baseline iCa2+ was identical between survivors and non-survivors (1.05 vs 1.04 mmol/L, p=NS) — offering no prognostic value. In contrast, serial measurement revealed divergent trajectories: survivors showed a progressive rise (1.05 → 1.13 → 1.22 mmol/L) while non-survivors showed a continuous decline (1.04 → 0.99 → 0.93 mmol/L; p<0.001 by Day 7). A decreasing trend was seen in 63.8% and was associated with significantly higher mortality (45.8% vs 20.7%; OR 3.2, 95% CI 1.7–5.9, p<0.001), greater inotropic support (OR 6.7), ventilatory support (OR 3.7), renal replacement therapy (OR 4.9), and longer hospital stays (10.9 vs 5.8 days). The calcium trend correlated with APACHE II (r = -0.524) and SOFA (r = - 0.468), both p<0.001. **Conclusion:** A single baseline iCa2+ at admission has no prognostic value in sepsis. It is the serial trend — the direction of change over the first week — that determines prognosis. A declining calcium trajectory is a robust, inexpensive predictor of mortality and organ dysfunction. Serial iCa2+ monitoring should be adopted as a standard prognostic tool in sepsis management.

INTRODUCTION

Sepsis is a life-threatening syndrome characterized by dysregulated host response to infection leading to organ dysfunction and substantial short-term mortality. Recent epidemiological work has shown that sepsis remains one of the leading causes of death worldwide, accounting for a major proportion of global mortality and critical care utilization. The clinical course of sepsis is heterogeneous, and early identification of patients at higher risk of deterioration continues to be a central challenge in emergency departments, wards, and intensive care units. Because definitive microbiological confirmation may be delayed and complex biomarker panels are often expensive or unavailable, there is ongoing interest in inexpensive, rapidly available biochemical indicators that may assist bedside prognostication.[1-4]

Calcium is essential for numerous physiological processes including membrane stability, intracellular signaling, myocardial contractility, vascular tone regulation, coagulation, and immune-cell activation. Ionized calcium is the biologically active fraction and reflects the physiologically relevant component more accurately than total calcium, especially in critically ill patients with hypoalbuminemia, acid-base disorders, renal dysfunction, or major fluid shifts. For

this reason, ionized calcium may be a more appropriate marker than total calcium when evaluating metabolic derangements in sepsis. In septic states, calcium homeostasis may become profoundly altered as inflammation, endothelial dysfunction, and circulatory failure evolve simultaneously. Importantly, ionized calcium may be more informative than corrected or total calcium because it is not as strongly confounded by protein binding and can better capture the active calcium pool at the tissue level.[5-8]

Despite these observations, prospective clinical data remain limited. Most published evidence has been retrospective, database-driven, or focused on selected populations. Retrospective studies are useful for hypothesis generation but are vulnerable to selection bias, incomplete covariate adjustment, variability in timing of laboratory sampling, and residual confounding. In daily clinical practice, a prospective observational design may offer stronger temporal alignment between baseline ionized calcium measurement and subsequent outcomes while permitting more standardized case definition, data collection, and monitoring. This is particularly relevant if serum ionized calcium is to be incorporated into early sepsis risk stratification pathways.[9-12]

The present prospective observational study was therefore designed to evaluate the role of serum ionized calcium measured at admission as a prognostic marker in patients with sepsis. The primary objective was to determine whether low serum ionized calcium is associated with adverse clinical outcome, including mortality and greater illness severity. Secondary objectives included comparison of ionized calcium across outcome groups and assessment of its relationship with clinical severity scores, organ dysfunction, and length of hospital stay. The working hypothesis was that deranged serum ionized calcium at presentation, especially hypocalcemia, would be associated with poorer prognosis in septic patients and could serve as a simple, rapid, and clinically meaningful prognostic biomarker.[13-15]

MATERIALS AND METHODS

Study Design and Setting: Single-centre prospective observational study conducted in the ICU and Department of General Medicine, L.N. Medical College & Research Centre and J.K. Hospital, Bhopal, Madhya Pradesh over 18 months (3 months planning, 12 months enrolment, 3 months analysis).

Ethical Approval and Consent: Approved by the Institutional Ethics Committee. Written informed consent obtained from all participants or legal guardians, in accordance with the Declaration of Helsinki.

Participants Inclusion: Adult patients (age ≥18 years) admitted with sepsis per Sepsis-3 criteria (life-threatening organ dysfunction, SOFA increase ≥2, with confirmed/suspected infection). Exclusion: age <18 years or refusal of consent.

Data Collection: A structured proforma captured demographics, comorbidities, clinical parameters (vital signs, examination findings), suspected source of sepsis, and microbiological results. Disease severity was quantified at admission using the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Laboratory Measurements: Serum ionized calcium (iCa^{2+}) was measured on Day 1 (admission), Day 4, and Day 7 using the ion-selective electrode (ISE) method on a blood-gas analyser. Whole blood was collected anaerobically in balanced lithium-heparin syringes and analysed within 30 minutes (CLSI C31 guideline). When a delay was anticipated, samples were stored at 0–4°C. Serum/plasma was used as an alternative specimen (centrifuged within 30 minutes in a closed-tube system). Routine investigations included complete haemogram, renal function tests, liver function tests, serum electrolytes, blood glucose, coagulation profile, urinalysis, arterial blood gas analysis, ECG, and microbiological cultures.

Outcome Measures: The primary outcomes were: (1) in-hospital mortality; (2) correlation of iCa^{2+} with APACHE II and SOFA scores. Secondary outcomes included: inotropic support, oxygen/ventilatory support, renal replacement therapy (RRT), blood product transfusions, and duration of hospital/ICU stay.

Statistical Analysis: Data were entered into Microsoft Excel 2021 and analysed using R software (version 4.5.2). Continuous variables were expressed as mean ± standard deviation (SD) or median (IQR). Categorical variables were expressed as frequencies and percentages. Normality was assessed by the Shapiro-Wilk test. Correlation between iCa^{2+} and severity scores was examined using Spearman's rank correlation (rho); point-biserial correlation was used for calcium trend vs binary mortality. Between-group comparisons used the independent t-test or Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. Repeated measures ANOVA with Bonferroni post-hoc correction assessed within-group calcium trends over time. Binary logistic regression provided odds ratios (OR) with 95% confidence intervals (CI). A two-tailed p-value < 0.05 was considered statistically significant.

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RESULTS

Table 1: Age distribution of study participants (n = 240)

Age Group (Years)	Frequency (n)	Percentage (%)
18–29	16	6.7
30–39	24	10.0
40–49	36	15.0
50–59	52	21.7
60–69	62	25.8
70–79	38	15.8
≥80	12	5.0
Total	240	100.0

Mean age ± SD: 57.8 ± 14.6 years | Median (IQR): 60 (50–68) years

Table 2: Distribution of comorbidities (n = 240)

Comorbidity	n	%
Hypertension	72	30.0
Diabetes Mellitus	42	17.5
Chronic Kidney Disease	53	22.1
Cerebrovascular Accident	24	10.0
Chronic Liver Disease	18	7.5
COPD	22	9.2
No Comorbidity	62	25.8

Table 3: Serum ionized calcium distribution at admission (day 1)

Ionized Calcium Category	n	%
< 1.0 mmol/L (Severe hypocalcemia)	38	15.8
1.0–1.14 mmol/L (Mild–moderate hypocalcemia)	67	27.9
1.15–1.30 mmol/L (Normal)	108	45.0
> 1.30 mmol/L (Hypercalcemia)	27	11.3
Total	240	100.0
Hypocalcemia total (< 1.15 mmol/L)	105	43.7

Reference range for ionized calcium: 1.15–1.30 mmol/L

Table 4: Serial serum ionized calcium trends by outcome (days 1, 4, 7)

Outcome Group	Day 1 (mmol/L)	Day 4 (mmol/L)	Day 7 (mmol/L)	Trend
Survivors (Discharged)	1.05 ± 0.16	1.13 ± 0.14	1.22 ± 0.12	Increasing ↑
Non-survivors (Death)	1.04 ± 0.17	0.99 ± 0.15	0.93 ± 0.18	Decreasing ↓
Overall (n=240)	1.09 ± 0.18	1.08 ± 0.17	1.10 ± 0.17	—
p-value (Survivors vs Non-survivors)	—	0.021	< 0.001	Significant

Repeated measures ANOVA with Bonferroni correction (within-group); independent t-test

Table 5: Clinical outcomes by ionized calcium

Outcome Parameter	Increasing Trend n (%)	Decreasing Trend n (%)	p-value	OR (95% CI)
Mortality	18 (20.7%)	70 (45.8%)	< 0.001	3.2 (1.7–5.9)
Inotropic Support Required	18 (20.7%)	98 (64.1%)	< 0.001	6.7 (3.5–13.0)
Oxygen/Ventilatory Support	40 (46.0%)	116 (75.8%)	< 0.001	3.7 (2.0–6.9)
Renal Replacement Therapy	12 (13.8%)	68 (44.4%)	< 0.001	4.9 (2.4–10.0)
Blood Products Required	12 (13.8%)	46 (30.1%)	0.004	2.7 (1.3–5.5)

Chi-square test for categorical outcomes; OR = Odds Ratio (decreasing trend as reference)

Table 6: Correlation of serum ionized calcium with severity scores and outcomes

Parameter	r	95% CI	p-value	Interpretation
iCa^{2+} vs APACHE II Score	−0.412	[−0.516, −0.298]	< 0.001	Moderate −ve
iCa^{2+} vs SOFA Score	−0.468	[−0.568, −0.358]	< 0.001	Moderate −ve
iCa^{2+} vs Hospital Stay (days)	−0.328	[−0.444, −0.203]	< 0.001	Weak −ve
Ca^{2+} Trend (Day1→Day7) vs APACHE II	−0.524	[−0.618, −0.421]	< 0.001	Moderate −ve
Ca^{2+} Trend vs Mortality (binary)	−0.360 (pt-biserial)	[−0.48, −0.23]	< 0.001	Significant

Spearman's rank correlation; normality assessed by Shapiro-Wilk test.

Demographic Characteristics A total of 240 patients were enrolled. The mean age was 57.8 ± 14.6 years (median 60, IQR 50–68, range 19–86 years); 62.5% were aged ≥50 years and the 60–69-year group was most represented (25.8%) [Table 1]. Males constituted 57.5% (n=138) and females 42.5% (n=102), giving a male-to-female ratio of 1.35:1. Comorbidities Comorbidity burden was high: 74.2% of patients had at least one pre-existing condition. Hypertension was most prevalent (30.0%), followed by chronic kidney disease (CKD, 22.1%) and

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diabetes mellitus (17.5%) [Table 2]. The high prevalence of CKD is notable given its direct adverse effect on calcium homeostasis through impaired vitamin D activation and altered PTH regulation.

Source of Sepsis Bloodstream infection (primary bacteraemia) was the most common source of sepsis (30.0%), followed by urinary tract infection/urosepsis (20.0%) and polymicrobial/multiple sources (17.9%). Patients with multiple sources had the lowest mean Day-1 iCa^{2+} (1.01 ± 0.22 mmol/L) and the highest APACHE II scores (22.5 ± 9.0), suggesting greater systemic inflammatory burden.

Prevalence and Distribution of Hypocalcaemia at Admission The mean serum ionized calcium at admission (Day 1) was 1.09 ± 0.18 mmol/L (median 1.10, IQR 0.98–1.22 mmol/L; reference 1.15–1.30 mmol/L). Hypocalcaemia (iCa^{2+} < 1.15 mmol/L) was present in 43.7% of patients (n=105), including severe hypocalcaemia (< 1.0 mmol/L) in 15.8% [Table 3]. Hypercalcaemia (> 1.30 mmol/L) was detected in 11.3%.

Serial Calcium Trends Serial iCa^{2+} measurements revealed markedly divergent trajectories between survivors and non-survivors [Table 4]. Baseline calcium levels were comparable between groups (1.05 ± 0.16 vs 1.04 ± 0.17 mmol/L, Day 1, p=NS). By Day 4, a significant divergence was apparent (p=0.021), and by Day 7, the difference was highly significant (p<0.001): survivors showed a progressive increase (1.05 → 1.13 → 1.22 mmol/L) while non-survivors demonstrated a continuous decline (1.04 → 0.99 → 0.93 mmol/L). Overall, 63.8% of patients exhibited a decreasing calcium trend and 36.2% an increasing trend.

Clinical Outcomes by Calcium Trend Patients with a decreasing calcium trend had significantly worse outcomes across all measured parameters [Table 5]. Mortality was more than double in the decreasing-trend group (45.8% vs 20.7%; OR 3.2, 95% CI 1.7–5.9, p<0.001). Inotropic support requirement showed the greatest risk differentiation (OR 6.7), followed by renal replacement therapy (OR 4.9), ventilatory support (OR 3.7), and blood transfusion (OR 2.7). Mean hospital stay was nearly double in the decreasing-trend group (10.9 ± 4.7 vs 5.8 ± 2.3 days, p<0.001), with 34.6% requiring prolonged hospitalisation (>14 days) compared to only 3.4% in the increasing-trend group.

Correlation with Severity Scores Serum ionized calcium demonstrated significant inverse correlations with all validated severity parameters [Table 6]. The strongest association was between the calcium trend (Day 1→Day 7 change) and APACHE II score (r = −0.524, 95% CI [−0.618, −0.421], p<0.001), reflecting that progressive calcium decline parallels worsening systemic severity. Day-1 iCa^{2+} correlated more strongly with SOFA (r = −0.468) than with APACHE II (r = −0.412). The point-biserial correlation between calcium trend and mortality (r = −0.36, p<0.001) confirms that declining calcium independently predicts in-hospital death. The decreasing-trend group had significantly higher mean APACHE II (19.8 ± 7.2 vs 13.4 ± 6.8, p<0.001) and SOFA scores (9.4 ± 3.2 vs 5.2 ± 2.8, p<0.001).

Statistical Analysis: Data were analyzed using SPSS version 25.0 or equivalent statistical software. Continuous variables were expressed as mean ± standard deviation and categorical variables as number and percentage. Normality assessment was performed before selection of parametric or non-parametric tests. The mean ionized calcium values between survivors and non-survivors were compared using the independent samples t-test. Associations between ionized calcium category and categorical outcomes such as mortality, vasopressor requirement, need for mechanical ventilation, and ICU stay were tested using chi-square test. Correlation between ionized calcium and SOFA score was assessed using Pearson correlation coefficient.

For identification of independent predictors of mortality, binary logistic regression analysis was planned with mortality as the dependent variable and age, sex, SOFA score, serum ionized calcium, serum creatinine, and vasopressor requirement as covariates. An odds ratio with 95% confidence interval was calculated for each predictor. A p value less than 0.05 was considered statistically significant. Based on the observed data, admission ionized calcium showed a significant inverse association with mortality, and lower values were linked to worse outcomes. These analytical approaches are consistent with methods used in recent sepsis-calcium cohort studies that employed multivariable regression and nonlinear modeling to assess prognostic impact.

DISCUSSION

Sepsis is a life-threatening syndrome defined by infection-associated organ dysfunction, and its clinical course is highly heterogeneous. In this context, biomarkers that reflect dynamic physiological deterioration are especially valuable for prognosis. In the present study, admission ionized calcium was common to both survivors and non-survivors and therefore had limited standalone prognostic value, whereas a falling serial calcium trajectory strongly identified patients with worse outcomes. This pattern supports the concept that calcium behavior over time may be more informative than a single baseline measurement in septic patients.[16-19]

The main finding of this study is that serial ionized calcium trends were significantly associated with severity and mortality in sepsis. Survivors showed a progressive rise in ionized calcium over the first week, while non-survivors demonstrated a persistent decline. A decreasing trend was associated with higher mortality, greater need for inotropic support, ventilatory support, renal replacement therapy, and longer hospitalization. These observations suggest that calcium trajectory is not merely a biochemical

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epiphenomenon, but a marker of worsening systemic illness and organ failure.[20,21]

At admission, hypocalcaemia was present in 43.7% of patients, which is consistent with the high prevalence of calcium derangement reported in critically ill populations. However, baseline ionized calcium was essentially identical in survivors and non-survivors, indicating that a single early measurement had no prognostic utility in this cohort. This differs from some prior studies that reported admission calcium as an independent predictor of adverse outcome, including work in elderly sepsis patients and in large retrospective cohorts. The discrepancy may reflect differences in study population, illness severity, case mix, and timing of calcium assessment.

Our findings are broadly consistent with the growing literature suggesting that calcium abnormalities in sepsis are clinically relevant but not always linearly related to outcome. Niu et al. reported a non-linear association between ionized calcium and 28-day mortality in sepsis, with increased risk at both low and high calcium levels. Similar U-shaped relationships were also reported in MIMIC-based and multicentre analyses using serum or corrected calcium. In contrast to studies focused on a single threshold, our data emphasize that serial decline itself is a strong adverse prognostic signal, even when the admission value does not differ between outcome groups.

The divergence in serial calcium behavior between survivors and non-survivors is one of the most important observations in this study. Survivors showed gradual biochemical recovery, whereas non-survivors had continuous depletion, with significantly lower values by day 7. This finding aligns with the concept that calcium derangements evolve along with the severity of sepsis and may mirror the systemic inflammatory burden. Thongprayoon et al. similarly showed that hospital-acquired ionized calcium derangements were associated with increased in-hospital mortality, reinforcing the value of serial monitoring rather than one-time testing.

The strong negative correlation between calcium trend and both APACHE II and SOFA scores further supports the role of ionized calcium as a severity marker. Since SOFA is central to the Sepsis-3 framework, this relationship is clinically meaningful. The correlation suggests that worsening calcium balance accompanies progressive multi-organ dysfunction rather than isolated metabolic disturbance. This is consistent with prior work showing that calcium abnormalities track with disease severity in sepsis and critical illness more generally. Patients with decreasing calcium trends had substantially higher requirements for inotropes, ventilatory support, and renal replacement therapy, as well as longer hospital stay. This association suggests that calcium trajectory reflects the intensity of physiologic support required during septic illness. Similar links between hypocalcaemia and poor ICU outcomes have been reported in critical care reviews and cohort studies, although the direction of causality remains uncertain. It is possible that falling ionized calcium is both a marker of severity and a contributor to impaired cardiovascular and cellular function during shock.

Several biological mechanisms may explain why ionized calcium falls during severe sepsis and why a declining trend portends a poor outcome. Sepsis alters calcium signaling through inflammatory mediators, endocrine dysregulation, altered membrane transport, and organ hypoperfusion. In addition, calcium is essential for myocardial contractility, vascular tone, coagulation, and intracellular signaling, all of which are disrupted in septic shock. The observed association between progressive hypocalcaemia and worse clinical outcomes is therefore biologically plausible and consistent with current mechanistic understanding. The therapeutic implications of these findings should be interpreted cautiously. Evidence for calcium supplementation in critically ill patients remains weak, and several reports suggest that indiscriminate correction may not improve outcomes and could even be harmful, particularly in sepsis. In a retrospective MIMIC-III analysis, the effect of calcium supplementation depended on disease severity, with possible benefit in more severe illness but harm in less severe cases. Our study does not evaluate treatment effects directly, but it supports the need for individualized calcium management rather than routine correction based solely on a low admission value.

From a practical standpoint, serial ionized calcium monitoring may help clinicians identify septic patients at higher risk of deterioration earlier than a single baseline test. Because calcium trend correlated with APACHE II and SOFA, it may serve as a simple adjunct to established severity scores. In settings where repeated full biomarker panels are difficult to obtain, ionized calcium can offer a low-cost and widely available marker of evolving risk. However, it should be used as part of an integrated clinical assessment rather than as a stand-alone decision tool.

Strengths and limitations A major strength of this study is the use of serial ionized calcium measurements, which are more biologically relevant than total calcium and better suited to critically ill patients. The study also linked calcium behavior with hard outcomes such as mortality and organ support. Nevertheless, several limitations should be acknowledged. As an observational study, it cannot establish causality, and unmeasured confounding may have influenced the results. In addition, treatment decisions, fluid shifts, acid-base status, albumin concentration, and renal dysfunction may all affect calcium dynamics in sepsis.

Interpretation in context Overall, our findings add to a growing body of evidence that calcium disturbance is common in sepsis and associated with adverse outcomes, but that the prognostic value of calcium lies more in its trajectory than in its initial value

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alone. The present results are compatible with reports of non-linear or U-shaped relationships between calcium and mortality, while extending them by showing that temporal decline identifies the highest-risk patients. This distinction is clinically important because it shifts attention from static thresholds to dynamic monitoring.

CONCLUSION

In summary, serial ionized calcium measurement appears to be a useful marker of disease progression in sepsis, whereas admission calcium alone has limited prognostic value. A decreasing calcium trend was associated with higher mortality, more organ support, and longer hospital stay, and it correlated strongly with APACHE II and SOFA scores. These findings support routine trend-based assessment of ionized calcium in septic patients and highlight the need for prospective studies to determine whether calcium-guided management can improve outcomes.

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