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Evaluation of Serum Ionized Calcium as a Prognostic Marker for Neonatal Sepsis

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Abstract

Background: Neonatal sepsis (NS) is a leading cause of morbidity and mortality in newborns, with early diagnosis being crucial for improving outcomes. Serum ionized calcium (iCa) has been suggested as a potential prognostic marker, as abnormal iCa levels, particularly hypocalcemia, are commonly observed in septic neonates and may correlate with disease severity and outcomes. **Aim:** To investigate the role of serum iCa as a prognostic marker for NS. **Patients and Methods**: This case-control study was conducted at Benha University Hospital and Benha Children's Hospital, involving 50 full-term infants diagnosed with NS (Group A) and 25 age- and sex-matched healthy controls (Group B). Infants having congenital anomalies or a history of exchange transfusions were excluded. The study aimed to investigate several factors, including thorough history taking, clinical evaluation, hematological tests, blood cultures, blood gas analysis, and serum calcium levels. Ethical approval was granted, and informed consent was obtained from all participants' parents. Additionally, laboratory analyses were conducted to explore the role of iCa as a potential prognostic marker for NS. **Results:** Neonates with sepsis had significantly lower serum iCa levels than controls, with iCa demonstrating a negative correlation with the hematological scoring system. ROC curve analysis indicated a strong predictive ability of iCa for mortality, with an AUC of 0.856 (95% CI: 0.742–0.969) and a cutoff of ≤0.78 mg/dL, yielding sensitivity and specificity of 81.82% and 89.29%, respectively. Additionally, iCa predicted the need for mechanical ventilation, with an AUC of 0.724 (95% CI: 0.575–0.874). Multivariate analysis confirmed that iCa remained significantly associated with mortality (OR = 0.031, P = 0.003) after adjusting for other clinical factors, underscoring its potential as a prognostic marker in NS. **Conclusion:** This study highlights the critical impact of iCa as a potential biomarker for predicting mortality and the need for mechanical ventilation in neonates with sepsis. Our findings demonstrate that decreased iCa levels are strongly associated with adverse outcomes, including increased mortality and prolonged need for respiratory support. iCa can be an excellent tool for early identification of high-risk neonates. Additionally, iCa levels were significantly correlated with various biochemical and hematological parameters, suggesting its potential role in reflecting the overall physiological state in septic neonates.

Keywords: neonatal, sepsis, ionized, calcium.

Introduction

Neonatal sepsis (NS) continues to be a major contributor to morbidity and mortality among newborns worldwide, particularly affecting preterm infants and those with low birth weight. This condition is characterized by a systemic infection accompanied by an inflammatory response, which, if not promptly identified and treated, can escalate to multi-organ failure, posing a severe threat to neonatal health. Despite significant advancements in neonatal care, including improved antimicrobial therapies and enhanced supportive interventions, the prevalence of NS remains alarmingly high, with mortality rates reported to range between 11% and 19% [1]. One of the most pressing challenges in managing NS is the difficulty in early diagnosis. The symptoms of NS are often nonspecific and can resemble other neonatal conditions, leading to potential delays in detection. Moreover, the rapid progression of sepsis further complicates its clinical management [2].

Over time, various biomarkers have been extensively investigated for their potential role in the diagnosis and prognosis of NS. Some of the most frequently studied biomarkers include C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6. These markers have shown clinical utility in certain contexts; however, variations in their patterns of elevation and normalization reduce their overall reliability as definitive early diagnostic or prognostic tools. Consequently, there remains an ongoing need to explore additional biomarkers that may offer more consistent and accurate prognostic value for NS [3].

Among the emerging biomarkers, serum ionized calcium (iCa) has attracted increasing attention as a potential indicator of NS. Research has consistently demonstrated that neonates with sepsis commonly exhibit hypocalcemia, specifically a decrease in serum iCa levels [4]. iCa, the biologically active form of calcium, is essential for several critical physiological functions, including the activation of enzymes in the coagulation cascade, neurotransmission, cellular signaling, and muscle contraction [5]. The development of hypocalcemia in septic neonates is thought to result from multiple factors, including the release of inflammatory cytokines that disrupt calcium homeostasis. Additionally, other conditions such as prematurity, hypoxia, and maternal diabetes have also been associated with alterations in calcium levels in neonates affected by NS [6].

Regarding the potential correlation between NS and serum iCa levels, there is growing interest in determining the potential of iCa as a prognostic marker for this condition. If proven reliable, serum iCa could serve as a valuable clinical tool for the early detection and management of NS. However, despite increasing research interest in this marker, its precise role in predicting disease severity and clinical outcomes remains insufficiently explored. Therefore, the present investigation aims to evaluate the prognostic significance of serum iCa in neonatal sepsis, providing insights into its potential utility in predicting disease progression and improving clinical outcomes.

PATIENTS AND METHODS

This case-control study was conducted at Benha University Hospital and Benha Children's Hospital, involving 50 full-term neonates diagnosed with NS (Group A) and 25 age- and sex-matched healthy controls (Group B). Participants were selected from the Pediatrics and Neonatology Departments of both hospitals, with eligibility criteria including full-term neonates with NS, while those with congenital anomalies or a history of exchange transfusions were excluded.

Ethical approval was obtained from the Pediatrics and Neonatology Department, the Research Ethics Committee of Banha Faculty of Medicine, and hospital administrators. Parental informed consent was secured, ensuring clarity regarding the study's objectives, methodology, and confidentiality.

Detailed maternal, perinatal, and neonatal histories were recorded, covering pregnancy complications, delivery mode, amniotic fluid characteristics, birth weight, APGAR scores, and early feeding patterns. Each neonate underwent a thorough physical examination, including assessments of vital signs and systemic evaluations of the cardiovascular, respiratory, gastrointestinal, and skin systems for clinical signs of NS.

Laboratory investigations included venous blood sampling for hematological and biochemical assessments. A complete blood count (CBC) with differential and the Hematological Scoring System (HSS) were used to evaluate NS severity. A significant neutrophil left shift was defined as an immature-to-total neutrophil ratio >0.2. The HSS considered parameters such as WBC count (<5000 or >20,000/mm³), platelet count (<150,000/mm³), absolute neutrophil count (<1500 or >7500/mm³), nucleated red blood cells, and neutrophil morphology abnormalities like toxic granulations and vacuolations [4].

CRP levels were measured using nephelometric immunoassay, with values >10 mg/L considered elevated. Blood cultures were obtained under sterile conditions for bacterial identification, with positive cultures confirming NS. Arterial blood gas (ABG) analysis was conducted to assess acid-base balance and oxygenation.

Serum calcium levels, including total serum calcium (measured via automated colorimetric methods) and iCa (assessed using an ion-selective electrode technique), were analyzed. Hypocalcemia was defined as total calcium levels below 8 mg/dL and iCa levels below 1.1 mmol/L (or <0.78 mg/dL).

Data and statistical analysis

The dataset was systematically reviewed, coded, and analyzed using IBM SPSS Statistics software. Data normality was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were reported based on data type: parametric data as mean ± standard deviation, non-parametric data as median and range, and categorical variables as frequency and percentage. Comparisons between groups were conducted using various statistical tests. The Student's t-test was used for parametric variables, the Mann-Whitney U test for non-parametric variables, and the Kruskal-Wallis test for multi-group comparisons. Categorical data were analyzed using the Chi-Square or Fisher's exact test. Correlation analysis examined relationships between quantitative variables, while the Receiver Operating Characteristic (ROC) curve evaluated diagnostic performance. Additionally, linear regression analysis was performed to identify potential risk factors. Statistical significance was set at $P \leq 0.05$ with a 95% confidence interval. [7].

RESULTS

Maternal characteristics of the studied groups

Maternal characteristics were comparable between cases and controls, including gestational age, mode of delivery, and maternal risk factors (P = 0.804, 0.854, 0.674, respectively). Table 1

Table 1: Maternal characteristics of the studied groups

	Cases (n = 50)	Controls (n = 25)	P-value
Gestational age (weeks)	38 ±1	38 ±1	0.804
Mode of delivery			
NVD	13 (26)	7 (28)	0.854
CS	37 (74)	18 (72)	
Maternal risk factors			
PROM	9 (18)	3 (12)	0.674
DM	5 (10)	4 (16)	
HTN	5 (10)	1 (4)	
UTI	13 (26)	5 (20)	
Placenta Previa	1 (2)	0 (0)	
DM+HTN	2 (4)	0 (0)	

Data is presented as Mean ±SD or frequency (%) NVD: Normal Vaginal Delivery, CS: Cesarean Section, PROM: Premature Rupture of Membranes, DM: Diabetes Mellitus, HTN: Hypertension, UTI: Urinary Tract Infection, *: Significant P-value.

Neonatal characteristics of the studied groups

Cases had significantly elevated body temperatures, increased heart rates, and lower random blood sugar levels (P = 0.019, 0.016, 0.002, respectively). Additionally, hypotension was significantly more frequent in cases compared to controls (P < 0.001). However, sex, weight, and age of onset were comparable between groups (P = 0.412, 0.375, 0.529, respectively). Table 2

Table 2: Neonatal characteristics of the studied groups

	Cases (n = 50)	Controls (n = 25)	P-value
Neonatal Sex			
Males	29 (58)	12 (48)	0.412
Females	21 (42)	13 (52)	
Weight (kg)	3.2 ±0.5	3.1 ±0.4	0.375
Temperature (°C)	37.4 ±0.7	37.1 ±0.4	**0.019***
HR (bpm)	145 ±18	135 ±15	**0.016***
RBS (mg\dl)	83 ±16	97 ±21	**0.002***
Blood Pressure			
Normal	22 (44)	25 (100)	**<0.001***
Hypotensive	28 (56)	0 (0)	
Age of onset (days)	5 (1 - 27)	2 (1 - 26)	0.529

Data is presented as Mean ±SD or frequency (%) or median (range). GA: Gestational Age, SD: Standard Deviation, HR: Heart Rate, bpm: Beats Per Minute, RBS: Random Blood Sugar, *: Significant P-value.

Immature neutrophils were significantly elevated in cases compared to controls (450 vs. 214 cells/μL, P < 0.001). CRP, urea, creatinine, AST, and ALT levels were also significantly higher (80 vs. 10 mg/L, 69 vs. 20 mg/dL, 1.6 ± 0.3 vs. 0.6 ± 0.2 mg/dL, 89 vs. 32 units/L, 97 vs. 16 units/L; P < 0.001, respectively). Conversely, hemoglobin levels and platelet counts were significantly lower in cases (12.7 ± 1.8 vs. 14.5 ± 1.4 g/dL, 80 vs. 380 × 10^3/μL; P < 0.001, respectively). Total and ionized calcium levels were also significantly reduced (8.2 ± 0.8 vs. 9.9 ± 0.7 mg/dL, 0.77 ± 0.07 vs. 1.09 ± 0.08 mg/dL; P < 0.001, respectively). Additionally, the hematological scoring system was significantly higher in cases (6 vs. 2, P < 0.001), with metabolic and respiratory acidosis occurring more frequently (P < 0.001). However, WBC count, neutrophils, lymphocytes, sodium, and potassium levels were comparable between groups (P = 0.581, 0.203, 0.074, 0.625, 0.678, respectively). Table 3

Table 3: Laboratory findings of the studied groups

	Cases (n = 50)	Controls (n = 25)	P-value
WBCs (n/L)	6500 (2000 - 40000)	15000 (8700 - 25200)	0.581
Neutrophils (cells/µL)	3750 (1500 - 21000)	7000 (4000 - 20000)	0.203
Mature N	3278 (1090 - 19000)	6800 (3800 - 19700)	0.122
Immature N	450 (0 - 2500)	214 (180 - 354)	**<0.001***
Lymphocytes	2750 (500 - 15800)	5700 (3000 - 8800)	0.074
Hb (g/dl)	12.7 ±1.8	14.5 ±1.4	**<0.001***
Platelets (10^3/ µL)	80 (20 - 150)	380 (245 - 450)	**<0.001***
CRP (mg/L)	80 (40 - 120)	10 (0 - 50)	**<0.001***
Hematological scoring system	6 (4 - 9)	2 (0 - 3)	**<0.001***
Urea (mg/dL)	69 (40 - 133)	20 (11 - 50)	**<0.001***
Creat. (mg/dL)	1.6 ±0.3	0.6 ±0.2	**<0.001***
AST (units/L)	89 (50 - 432)	32 (15 - 65)	**<0.001***
ALT (units/L)	97 (45 - 321)	16 (11 - 40)	**<0.001***
ABG			
Respiratory acidosis	23 (46)	8 (32)	**<0.001***
Metabolic acidosis	26 (52)	2 (8)	
Respiratory alkalosis	1 (2)	0 (0)	
Na (mEq/L)	141 ±9	141 ±5	0.625
K (mEq/L)	4.7 ±0.5	4.8 ±0.4	0.678
Total Ca (mg/dl)	8.2 ±0.8	9.9 ±0.7	**<0.001***
Ionized Ca (mg/dl)	0.77 ±0.07	1.09 ±0.08	**<0.001***

Data is presented as Mean ±SD or frequency (%) or median (range). WBCs: White Blood Cells, SD: Standard Deviation, Hb: Hemoglobin, CRP: C-Reactive Protein, Creat.: Creatinine, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ABG: Arterial Blood Gas, Na: Sodium, K: Potassium, Ca: Calcium, *: Significant P-value.

The use of inotropes was significantly elevated in cases compared to controls (90% vs. 12%, P < 0.001). Cases also required more invasive respiratory support, with a significantly elevated proportion on mechanical ventilation (86% vs. 12%, P < 0.001), while nasal support and CPAP were more common in controls (P < 0.001). Mortality was significantly elevated in cases, with 44% non-survivors compared to 4% in controls (P < 0.001). However, the NICU stay duration was comparable between cases and controls (P = 0.105). Neonates with sepsis were classified according to prognosis into survivors (n = 28) and non-survivors (n = 22).

Maternal and neonatal characteristics of sepsis neonates according to survival status

Gestational age, mode of delivery, and maternal risk factors did not differ significantly between the groups (P = 0.622, 0.640, 0.640 respectively). However, survivors had a significantly later age of onset (12 vs. 2 days, P = 0.043) and higher body temperatures (37.6 ± 0.8 vs. 37.1 ± 0.5°C, P = 0.033). Other factors, including sex, birth weight, heart rate, random blood sugar, and blood pressure, were comparable (P = 0.111, 0.093, 0.973, 0.165, 0.335 respectively).

Laboratory findings of sepsis neonates according to survival status

Survivors exhibited higher potassium (4.9 ± 0.5 vs. 4.5 ± 0.5 mEq/L, P = 0.008) and ionized calcium levels (0.81 ± 0.05 vs. 0.72 ± 0.06 mg/dL, P < 0.001). However, other laboratory parameters showed no significant differences between the groups, including WBC count, neutrophils, lymphocytes, hemoglobin, platelets, CRP, hematological scoring system, urea, creatinine, AST, ALT, sodium, and total calcium (P = 0.637, 0.798, 0.434, 0.399, 0.537, 0.179, 0.92, 0.725, 0.88, 0.406, 0.71, 0.402, 0.439 respectively). Additionally, acid-base status was comparable (P = 0.658). (Table 4).

Table 4: Laboratory findings of sepsis neonates according to survival status

	Survivors (n = 28)	Non-survivors (n = 22)	P-value
WBCs (n/L)	6500 (3000 - 30000)	10000 (2000 - 40000)	0.637
Neutrophils (cells/µL)	3750 (1500 - 20000)	3600 (1500 - 21000)	0.798
Mature N	3278 (1300 - 19000)	3293 (1090 - 18900)	0.792
Immature N	475 (0 - 2500)	436 (0 - 2500)	0.456
Lymphocytes	2800 (1000 - 14000)	1800 (500 - 15800)	0.434
Hb (g/dl)	12.9 ±1.7	12.5 ±1.8	0.399
Platelets (10^3/µL)	90 (30 - 150)	75 (20 - 140)	0.537
CRP (mg/L)	90 (40 - 120)	73 (40 - 120)	0.179
Hematological scoring system	6 (4 - 8)	6 (4 - 9)	0.92
Urea (mg/dL)	69 (40 - 122)	71 (45 - 133)	0.725
Creat. (mg/dL)	1.6 ±0.2	1.6 ±0.3	0.88
AST (units/L)	86 (50 - 244)	105 (50 - 432)	0.406
ALT (units/L)	98 (45 - 211)	90 (47 - 321)	0.71
ABG			
Respiratory acidosis	13 (46.4)	10 (45.5)	0.658
Metabolic acidosis	14 (50)	12 (54.5)	
Respiratory alkalosis	1 (3.6)	0 (0)	
Na (mEq/L)	140 ±7	142 ±10	0.402
K (mEq/L)	4.9 ±0.5	4.5 ±0.5	**0.008***
Total Ca (mg/dl)	8.3 ±0.9	8.1 ±0.8	0.439
Ionized Ca (mg/dl)	0.81 ±0.05	0.72 ±0.06	**<0.001***

Data is presented as Mean ±SD or frequency (%) or median (range). WBCs: White Blood Cells, Hb: Hemoglobin, CRP: C-Reactive Protein, Creat.: Creatinine, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ABG: Arterial Blood Gas, Na: Sodium, K: Potassium, Ca: Calcium, *: Significant P-value.

Neonatal outcomes according to survival status

NICU stay duration, use of inotropes, and types of respiratory support were comparable between the two groups (P = 0.369, 0.386, 0.211 respectively).

Correlations between serum ionized Ca with laboratory parameters

iCa showed significant positive correlations with hemoglobin, potassium, and total calcium (P = 0.018, 0.006, 0.026 respectively). Conversely, significant negative associations were observed with creatinine, sodium, urea, aspartate aminotransferase, and alanine aminotransferase (P = 0.013, 0.044, 0.033, 0.005, 0.029 respectively).

No significant relationships were found with random blood sugar, white blood cell count, neutrophils, mature neutrophils, immature neutrophils, lymphocytes, platelets, or CRP(P = 0.992, 0.651, 0.397, 0.49, 0.311, 0.458, 0.1, 0.959 respectively).

Table 5:Correlations between serum ionized Ca with laboratory parameters

	Ionized Ca (mg/dl)	
	r	**P-value**
RBS (mg\dl)	-0.002	0.992
Hb (g/dl)	0.333	**0.018***
Creat. (mg/dL)	-0.348	**0.013***
Na (mEq/L)	-0.286	**0.044***
K (mEq/L)	0.382	**0.006***
Total Ca (mg/dl)	0.316	**0.026***
WBCs (n/L)	-0.066	0.651
Neutrophils (cells/µL)	-0.122	0.397
Mature N	-0.1	0.49
Immature N	-0.146	0.311
Lymphocytes	0.107	0.458
Platelets (10^3/µL)	0.235	0.1
CRP (mg/L)	0.007	0.959
Urea (mg/dL)	-0.302	**0.033***
AST (units/L)	-0.391	**0.005***
ALT (units/L)	-0.309	**0.029***

iCa levels exhibited a significant negative correlation with the hematological scoring system (r = -0.329, P = 0.02). However, no significant associations were identified with gestational age, birth weight, heart rate, body temperature, age at disease onset, or NICU stay duration (P = 0.864, 0.396, 0.175, 0.629, 0.947, 0.576 respectively).

ROC curve analysis demonstrated that serum iCa serves as a strong mortality predictor in ABB, with a significant AUC of 0.856 (95% CI: 0.742–0.969). The most effective threshold for predicting mortality was an iCa level of ≤0.78 mg/dL, with sensitivity, specificity, PPV, and NPV of 81.82%, 89.29%, 85.7%, and 86.2%, respectively (P < 0.001).

Neonates requiring MV had significantly lower serum iCa levels than those who did not (0.76 ± 0.07 vs. 0.81 ± 0.04 mg/dL, P = 0.011). ROC curve analysis assessing iCa's predictive value for MV use showed an AUC of 0.724 (95% CI: 0.575–0.874), indicating moderate predictive ability. The optimal cutoff for predicting MV was ≤0.78 mg/dL, with sensitivity, specificity, PPV, and NPV of 48.84%, 100%, 100%, and 24.1%, respectively. However, the P-value of 0.059 suggested borderline statistical significance.

Multivariate analysis confirmed that serum iCa remained a significant independent predictor of mortality in ABB, even after adjusting for age at disease onset, body temperature, and serum potassium levels. The odds ratio (OR) was 0.031 (95% CI: 0.003–0.295, P = 0.003), underscoring its strong association with mortality in ABB.

Discussion

NS remains a predominant cause of mortality and morbidity among newborns, often leading to severe complications that may result in long-term disabilities. Research has established a strong association between NS and various conditions such as bronchopulmonary dysplasia, cerebral injury, retinopathy of prematurity, and necrotizing enterocolitis (NEC), all of which significantly impact neonatal health outcomes [8]. Given these risks, the identification of reliable biomarkers for assessing disease severity and predicting prognosis is crucial for improving clinical management strategies.

Inflammatory markers, including CRP and PCT, are commonly used in the diagnosis and monitoring of sepsis. However, both have notable limitations.When CRP, which is an acute-phase protein that is produced by the liver in response to infection, gradually increases, it becomes less efficient for early detection. Conversely, PCT, a glycoprotein secreted by extra-thyroidal tissues during systemic inflammation, exhibits a more rapid response, increasing within hours of infection onset and peaking between 6 and 12 hours, making it a useful early indicator of sepsis [9]. Despite this advantage, PCT levels can vary depending on neonatal age and may be influenced by non-infectious conditions such as respiratory distress syndrome and tissue injury, which can reduce its specificity as a sepsis marker [10].

Despite this advantage, PCT levels can vary depending on neonatal age and may be influenced by non-infectious conditions such as respiratory distress syndrome and tissue injury, which can reduce its specificity as a sepsis marker [11].

In this research, the diagnostic utility of iCa was investigated by the use of iCa in NS and its correlation with survival outcomes. This prospective case-control study involved 75 full-term neonates, comprising 50 neonates diagnosed with NS and 25 healthy, age- and sex-matched controls. The groups were comparable in terms of baseline characteristics, including gestational age, mode of delivery, maternal risk factors, sex distribution, birth weight, and age of symptom onset.

The study findings revealed that septic neonates exhibited significantly elevated body temperatures ($P = 0.019$) and heart rates ($P = 0.016$) compared to the control group. Additionally, hypotension was documented in 56% of septic neonates, whereas all control neonates maintained normal blood pressure ($P < 0.001$). These results underscore the systemic effects of sepsis, particularly its impact on cardiovascular stability. The autonomic nervous system plays a critical role in sepsis pathophysiology, regulating body temperature, respiratory function, heart rate, and blood pressure. While these physiological adjustments may initially serve as compensatory mechanisms, they can accelerate disease progression when homeostasis is disrupted [12-13].

Furthermore, blood glucose levels were significantly lower in septic neonates ($P = 0.002$), reflecting the metabolic instability commonly associated with sepsis. Hypoglycemia in NS is well-documented, with studies reporting variable occurrences of both hypoglycemia and hyperglycemia among septic patients [14-15]. Sepsis-induced hypoglycemia can be attributed to feeding difficulties, heightened metabolic demands, and hypothermia. Infected neonates often experience poor oral intake, and systemic inflammation increases energy consumption, exacerbating low blood glucose levels. Additionally, sepsis-related metabolic stress can impair glucose regulation, further aggravating hypoglycemia [16].

Laboratory results highlighted several significant differences between the sepsis and control groups. While WBC, mature neutrophils, neutrophil count, and lymphocytes did not differ significantly ($P > 0.05$), a notable increase in immature neutrophils was observed in the sepsis group ($P < 0.001$), indicative of a left shift, a well-recognized marker of sepsis (17-18). Moreover, CRP levels were significantly higher in septic neonates ($P < 0.001$), confirming the presence of an inflammatory response. Additionally, hemoglobin and platelet counts were markedly lower in the sepsis group ($P < 0.001$), and the hematological scoring system showed a significant elevation ($P < 0.001$), further reflecting the severity of the condition.

Sepsis was also found to significantly affect renal and liver function. Elevated urea and creatinine levels were observed in septic neonates ($P < 0.001$), alongside increased liver enzymes (AST and ALT) ($P < 0.001$). These findings are consistent with sepsis-related tissue hypoperfusion and inflammation, which contribute to multi-organ dysfunction, including renal and hepatic impairment (19). Hypocalcemia, a commonly reported phenomenon in septic patients, was observed in both total calcium and iCa levels, with significantly diminished values in the sepsis group than in the controls ($P < 0.001$). The mechanisms underlying sepsis-induced hypocalcemia are complex and multifactorial, involving calcium redistribution from the vascular compartment, impaired parathyroid function, and altered calcium homeostasis [20].

Further analysis revealed that the reductions in iCa levels were shown to be strongly associated with worse clinical outcomes. There was a significant difference in the levels of iCa between neonates who needed mechanical breathing and those who did not ($P = 0.011$). Furthermore, the study of the ROC curve revealed that serum iCa had a robust capacity to predict mortality due to neurosurgical conditions, as shown by an AUC value of 0.856 ($P < 0.006$). An important predictive biomarker for newborn sepsis might be iCa, according to these data, which suggest that it could be useful. Further reinforcement of its possible significance as a predictor of mortality risk in NS was provided by the fact that survivors in the study demonstrated considerably greater levels of iCa compared to non-survivors ($P < 0.001$) [11].

This research has a number of limitations, despite the fact that it offers some encouraging results. The generalizability of the findings may be limited due to the relatively small sample size, the methodology of the trial, which was conducted at a single institution, and the absence of long-term follow-up. In addition, while the research shows the potential of iCa as a biomarker for NS, it does not demonstrate a clear causative association between the levels of iCa and the course of sepsis. In order to confirm these results, continue investigating the mechanistic role that iCa plays in the pathophysiology of sepsis, and evaluate its potential as a therapeutic target in the treatment of NS, future research should concentrate on conducting bigger studies that include several centers. It is also necessary to conduct longitudinal studies in order to evaluate the long-term clinical consequences of calcium abnormalities in newborns who are recovering from sepsis.

CONCLUSION

The present study underscores the crucial role of iCa as a promising biomarker for predicting both mortality risk and the necessity for MV in neonates diagnosed with sepsis. Our findings indicate a strong association between reduced iCa levels and unfavorable clinical outcomes, including higher mortality rates and prolonged respiratory support. Notably, ROC curve analysis demonstrated that iCa serves as a highly reliable predictor of mortality in neonatal sepsis, with an AUC of 0.856, highlighting its potential as an effective tool for the early identification of high-risk neonates. Furthermore, iCa levels exhibited significant correlations with multiple biochemical and hematological parameters, suggesting its broader role in reflecting the overall physiological status of septic neonates.

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