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Sepsis-Induced Disruption in Parathormone-Cholecalciferol-Calcium Axis in Children from a Lower Middle-Income Country: A Prospective Observational Study

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Abstract

Background

Sepsis disrupts parathormone-cholecalciferol-calcium (PCC) axis. However, comprehensive longitudinal data from LMICs remain scarce. We aimed to characterize these disruptions and explore their correlation with critical care needs and outcomes in pediatric septic shock.

Methods

25-hydroxycholecalciferol [25(OH)D], parathormone, corrected total and ionized calcium (cTCa and iCa^{++}) were measured among children with septic shock (6mo-12yrs; n = 69) in a prospective observational study. 25(OH)D and parathormone were measured on day (D) 1 and D7, while cTCa and iCa^{++} were measured on D1, D4, D7, and D10. Levels and their trends over 10 days were compared between survivors and non-survivors. Correlation between D1 levels and illness severity indicators, resuscitation requirements, and outcomes was assessed.

Results

Eighteen (26.1%) patients were undernourished; mortality was 37.7% (26/69). Vitamin D insufficiency was common; 81.2% had 25(OH)D < 20ng/mL on D1, including 55.1% with deficiency (< 12ng/mL). Non-survivors had lower 25(OH)D on D1 and showed a sharp paradoxical rise on D7. Parathormone was elevated in 44.1% patients, with significantly higher levels among non-survivors on D1 and D7. Hypocalcemia was common (30.5% by cTCa; 59.4% by iCa^{++}). Non-survivors had lower cTCa on D1 that persisted over 10 days, whereas it gradually rose in survivors. Lower 25(OH)D and higher parathormone correlated with greater illness severity scores. Higher parathormone and lower calcium levels were associated with greater resuscitative requirements; the former was also correlated with poor clinical outcomes. A level > 53pg/mL predicted mortality (AUC, 0.662; p = 0.019).

Conclusions

Findings demonstrate a high burden of hypovitaminosis D, hypocalcemia, and marked disruption in PCC axis in pediatric septic shock, including persistent lower calcium levels despite continued secondary hyperparathyroidism among non-survivors. These disruptions were correlated with greater illness severity, higher critical care needs, and a poor prognosis. These derangements justify trials of vitamin D replacement, with or without calcium, for pediatric septic shock in LMICs.

INTRODUCTION

Sepsis affects approximately 25 million children globally [1]. Burden and mortality of pediatric sepsis are disproportionately high in low- and middle-income countries (LMICs) driven by multiple socioeconomic, infrastructural, and clinical challenges [1, 2]. Nearly one-third of septic shock children admitted to tertiary care hospitals of LMICs have undernutrition and multiple micronutrient deficiencies [3, 4, 5, 6]. Associated impairments in cellular, immune, and metabolic functions may contribute to the high morbidity and mortality [7, 8].

Ensuring universal access to septic shock resuscitation —based on correcting the demand-delivery imbalance of oxygen— to children of LMICs is ideal, and would be a long-term goal [9]. However, efforts should be made to identify easily modifiable metabolic risk factors to reduce pediatric sepsis mortality in the interim [10, 11, 12]. During sepsis, disruption of parathormone-cholecalciferol-calcium (PCC) axis leads to hypocalcemia, low parathormone and 1,25-dihydroxycholecalciferol (calcitriol) levels, even in vitamin D-sufficient subjects, and are mediated by calcium-sensing receptors (CaSRs) [13, 14]. Vitamin D (VitD) plays an important role in innate and adaptive immune responses and in endothelial and mucosal barrier functions through ubiquitously present calcitriol receptors (vitamin D receptors, VDRs) [15, 16]. CaSRs and VDRs seem to act as a critical intersection between systemic inflammation and calcium homeostasis. Hypocalcemia, low levels of 25-hydroxycholecalciferol [25(OH)D], and high and low levels of parathormone are associated with higher illness severity scores and poorer clinical outcomes in studies from apparently well-nourished populations [14, 15, 17].

The high prevalence of pre-existing hypovitaminosis-D (hypo-D) in critically ill children with sepsis from LMICs, its implicated role in poor outcomes, and potential for therapeutic intervention have increased interest in sepsis-induced PCC axis disruption (SIPCCAD) [6, 18–22]. Available studies usually measured one or two of serum calcium, vitamin D, and parathormone, and provided limited snapshots of SIPCCAD. There is only a handful of studies on simultaneous measurement of all three components of the PCC axis and on the replacement of calcium and VitD in pediatric sepsis, especially from regions with a high prevalence of hypo-D [9, 19, 23, 24]. Thus, a need is felt to generate more pathophysiological data and clinical evidence on the role of hypo-D and hypocalcemia in pediatric sepsis [9, 10]. We designed this prospective study to examine changes in parathormone, 25(OH)D, and calcium over the first 10 days in children with fluid-refractory septic shock, to compare these changes between survivors and non-survivors, and to examine their correlation with illness severity and clinical outcomes.

METHODS

Study Design, Clinical Setting, and Ethical Clearance: This single-center prospective cohort study was conducted in the Pediatric Emergency Room (PER) and the Pediatric Intensive Care Unit (PICU) of a tertiary care teaching hospital in a lower-middle-income country. It was part of a time-bound dissertation project. The study protocol was approved by the Institutional Ethics Committee (Intramural) vide letter no. INT/IEC/2019/002215 dated 15.10.2019. Research methods adhered to the Declaration of Helsinki (2024 version). The manuscript is reported according to the ‘Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Cohort Studies’.

Screening, Eligibility, and Consent

Children (age ≥ 6 months to < 12 years) with fluid-refractory septic shock were enrolled within 24 hours of documentation of shock during a 14-month period (November, 2019 to December, 2020). Fluid-refractory septic shock was defined as per the International Pediatric Sepsis Consensus Conference definition [25]. Patients with chronic liver or kidney disease, congenital heart disease, cardiomyopathy, endocrine disorders, non-nutritional rickets, chronic infections, autoimmune disorders, oncologic diseases, cerebral palsy or other chronic neurologic conditions, immunodeficiency states, inborn errors of metabolism, acute kidney injury, and shock due to diarrhea/dehydration were excluded. Exclusions also included patients on long-term corticosteroids or immunosuppressants, on calcium or VitD supplements, and who had received cardiopulmonary resuscitation before enrolment. Eligible patients were enrolled after written informed consent from their legal guardians.

Data Collection and Definitions

Baseline demographic and clinical data —including nutritional status [26], Pediatric Sequential Organ Failure Assessment (pSOFA) [27], fluid resuscitation, and vasoactive inotrope score (VIS) [28] —were recorded. In the authors' clinical setting, patients are usually managed in PER for an initial 24 hours or more before transfer to PICU. Thus, the Pediatric Risk of Mortality III (PRISM III) score was documented after 24 hours of stay in PER and upon transfer to PICU. Ionised calcium (iCa^{++}) was measured at admission, while total calcium, 25(OH)D, and parathormone levels were measured within 24 hours. Subsequently, total calcium and iCa^{++} were recorded on days 4, 7, and 10, while 25(OH)D and parathormone levels were repeated only on day 7, provided the patient remained admitted to the PICU. Serum albumin was usually measured twice a week. Albumin levels available on day 1(+ 1), day 4(± 1), day 7(± 1), and day 10(± 1) were considered to represent levels on day 1, day 4, day 7, and day 10, respectively, and were used to calculate corrected total calcium (cTCa). 25(OH)D level > 20ng/mL was considered as sufficient VitD status, while hypo-D was classified as VitD insufficient (12-20ng/mL) and VitD deficient (< 12ng/mL) [29]. Parathormone status was classified as low (< 10pg/mL), normal (10-65pg/mL), and High (> 65pg/mL) [30]. cTCa 8.5-10.7mg/dL and iCa^{++} ≥1.09mMol/L were considered normal. Mild to moderate hypocalcemia and severe hypocacemia were defined based on cTCa (7.0-8.4mg/dL and ≤ 6.9mg/dL, respectively) and iCa^{++} (0.80-1.09mMol/L and < 0.80mMol/L, respectively). Hypoalbuminemia was defined as serum albumin < 3.5 g/dL. Some patients leave hospital in a moribund state after being counselled about the irreversibility of the condition and futility of further care. These patients get categorized as Left Against Medical Advice (LAMA), and were considered equivalent to death [5].

Laboratory Measurements

iCa^{++} was measured using an ion-selective electrode method on an arterial blood gas analyzer (ABL800 Basic, Radiometer Medical ApS, Denmark). Total calcium was measured using the Arsenazo III method on a fully automated analyzer (AU5811, Beckman Coulter, USA). Plasma 25(OH)D was measured with

chemiluminescent immunoassay (CLIA), while intact parathormone (iPTH) was measured with a second-generation electrochemiluminescence immunoassay (ECLIA) (cobas® 8000, Roche Diagnostics, Germany).

Management and Clinical Monitoring

Patients were resuscitated as per standard guidelines, and subsequently managed according to the unit protocol for antimicrobial therapy, fluid therapy, vasoactive and inotropic support, oxygen and ventilatory management, blood transfusion, nutritional support, and sedo-analgesia. Intravenous calcium was given whenever iCa^{++} fell below 0.8mMol/L; the threshold was higher among patients with symptomatic hypocalcemia (iCa^{++} <1.0mMol/L).

Outcome Measures

Comparison of levels of 25(OH)D, parathormone, cTCa, and iCa^{++} on day 1 (D1) and their trends over 10 days between survivors and non-survivors were the primary outcome measures. Other outcome measures included correlation of D1 levels of 25(OH)D, parathormone, cTCa, and iCa^{++} with illness severity indicators, inotrope-free hours in 120 hours (IFH_{120}), acute care area-free days in 14 days ($ACAFD_{14}$), hospital-free days in 28 days (HFD_{28}), and mortality.

Statistical Analysis: A convenient sample size of 100 was planned; however, only 69 patients were enrolled due to COVID-19-related constraints. We missed 27 out of 212 (12.7%) opportunities to measure serum albumin (D1: 3/69; D4: 4/59; D7: 10/48; D10: 10/37). The probability of missing these values was unrelated to observed and unobserved data, and was classified as 'missing completely at random' [31]. Missing values were imputed with the median of available serum albumin values on the respective days of observations (i.e., D1, D4, D7, and D10). Continuous variables and categorical variables were analysed with Mann-Whitney U test and Chi-square test (or Fisher's exact test as appropriate) respectively. Within-group change over time in continuous variables was analysed with Wilcoxon test and Friedman test for two timepoints and for more than two timepoints, respectively, while within-group change over time in categorical variables was analysed with Cochran's Q test. Change over time between survivors and non-survivors was compared using Generalized Estimating Equations (GEE). Correlations were analysed with Spearman's correlation coefficient. A p-value < 0.05 was considered statistically significant. Analysis was done using SPSS Version 23 (IBM SPSS Statistics, Armonk, NY).

RESULTS

Figure 1 and Table 1 show the study flow diagram and the baseline demographic characteristics of enrolled patients, respectively. Non-survivors were younger than survivors (p = 0.36). Eighteen patients (26.1%) were undernourished, more among non-survivors [9/26 (34.6%) vs 9/43 (20.9%), p = 0.21]. Three patients had pre-infantile tremor syndrome, while none had clinical signs of hypo-D. Patients were symptomatic for a median of 5 days; non-survivors were ill for a relatively longer time (p = 0.038). 44

patients (63.8%) were referred after a median stay of 1 day in referring hospitals. Acute pyogenic infections (18, 26.1%), pneumonia (17, 24.6%), toxic shock syndrome (8, 11.6%), and tropical infections (e.g., scrub typhus, Dengue) (16, 23.2%) were common diagnoses. Twenty-one (30.4%) patients had positive cultures (Methicillin-sensitive *Staphylococcus aureus*, 6; Methicillin-resistant *Staphylococcus aureus*, 4; *Escherichia coli*, 3; *Klebsiella pneumoniae*, 2 and *Candida*, 2), while throat swabs were positive for H1N1 in two patients, and respiratory syncytial virus in one. Table 2 summarizes critical care characteristics of patients. Non-survivors had significantly higher illness severity scores than survivors. Though non-survivors had higher lactate at admission {3(1.9–4.2) vs 2.1(1.3–4.1), p = 0.11}, the significant difference was observed only in the maximum lactate level reported during the first 24 hours {3.9(2.7–5.9) vs 2.4(1.7–4.3); p = 0.018}. Non-survivors needed greater inotropic support throughout their clinical course. Seven patients (10.4%) developed culture-positive healthcare-associated infection during their PICU stay (*Acinetobacter baumannii*, 4; *Acinetobacter nosocomialis*, 1; *Pseudomonas aeruginosa*, 1, and *polymicrobial growth*, 1). Twenty-six (37.7%) patients had an adverse outcome (18 deaths; 8 LAMA).

Median 25(OH)D was 11.1(5.1–17.9) ng/mL on D1; eighteen (26.1%) patients had levels in the insufficient range, while 38 (55.1%) had levels in the deficient range **(**Fig. 2, **Supplementary Table 1)**. Non-survivors had lower 25(OH)D levels than survivors {9.9(3.6–17.0) vs 11.6(6.7–18.7), p = 0.47}. Levels increased significantly on D7 in patients who ultimately died (p = 0.016). Survivors did not show any change by 7 days **(**Fig. 3, **Supplementary Table 2)**. Though nutritional status did not affect 25(OH)D levels, undernourished patients had non-significant rise on D7 compared to D1 {16.1(9.1–22.6) vs 12.2(4.1–17), p = 0.41}, in contrast to stable levels among non-undernourished ones {12.4(9.2–18.5) vs 11.1(5.5–18.4), p = 0.84} (**Supplementary Table 3**). 25(OH)D on D1 was negatively correlated with PRISM III score in PER (ρ= -0.22, p = 0.064), pSOFA on D1 (ρ= -0.23, p = 0.062) and maximum pSOFA (ρ= -0.20, p = 0.097). It did not correlate with $ACAFD_{14}$, HFD_{28}, IFH_{120}, and mortality.

Parathormone levels were available for 68 patients on D1; the median was 55.1 (26.4-133.3) pg/mL. Thirty (44.1%) patients had values above the upper limit of normal (ULN), while more than half of patients (36/68, 52.9%) had values within reference range (Fig. 2, **Supplementary Table 1**). Non-survivors had significantly higher levels than survivors on D1 (p = 0.026) and continued to show higher levels even on D7 (Fig. 3, **Supplementary Table 2)**. Nutritional status did not affect parathormone levels on D1 nor the change in parathormone levels by D7 (**Supplementary Table 3**). The D1 parathormone levels were positively correlated with illness severity indicators, e.g., lactate at admission (ρ = 0.29, p = 0.018), PRISM III score in PER (ρ = 0.21, p = 0.088), pSOFA on D1 (ρ = 0.26, p = 0.033), and maximum pSOFA (ρ = 0.34, p = 0.005). These were also positively correlated with resuscitative requirements, e.g., volume of fluid bolus in the first 24 hours (ρ = 0.36, p = 0.002), VIS at 24 hours (ρ = 0.22, p = 0.065), maximum VIS (ρ = 0.42, p = 0.003), and time taken to reverse shock (ρ = 0.46, p = 0.001). The D1 parathormone levels were negatively correlated with IFH_{120} (ρ=-0.42, p < 0.001), $ACAFD_{14}$ (ρ=-0.37, p = 0.002), HFD_{28} (ρ=-0.36, p = 0.002), and were positively correlated with mortality ((ρ = 0.27, p = 0.025). The parathormone/25(OH)D

ratio on D1 mirrored the correlation trends observed for parathormone. A value ≥ 52.7pg/mL independently predicted mortality (AUC, 0.66; sensitivity, 73.1%; specificity, 61.9%; p = 0.019) (Fig. 4).

Twenty-one (30.4%) and 41 (59.4%) children had hypocalcemia based on cTCa and iCa^{++}, respectively (Fig. 2, **Supplementary Table 1**). Non-survivors had significantly lower cTCa on D1 than survivors (p = 0.012). Survivors demonstrated progressive improvement over 10 days (p < 0.001 for within-group change), while non-survivors revealed a declining trend (p = 0.021 for within-group change). Further, non-survivors had significantly lower cTCa at all time points (all p < 0.05) (Fig. 3, **Supplementary Table 2**). Analyses of measured total calcium gave results very similar to cTCa (data not shown). A similar trend was observed for iCa^{++}; however, the difference between survivors and non-survivors, and the change over time, were not statistically significant (Fig. 3, **Supplementary Table 2**). Nutritional status did not affect cTCa or iCa^{++} (**Supplementary Table 3**). cTCa was negatively correlated with volume of fluid boluses required in the first 6 hours (=-0.23, p = 0.056) and the first 24 hours (=-0.25, p = 0.037), VIS at 24 hours (=-0.35, p = 0.003), and maximum VIS required (ρ=-0.30, p = 0.011). iCa^{++} had negative correlation with maximum pSOFA (ρ=-0.24, p = 0.053), VIS at 24 hours (ρ=-0.30, p = 0.011) and maximum VIS required (ρ=-0.25, p = 0.034). Both cTCA and iCa^{++} were positively correlated with IFH_{120} (ρ = 0.25, p = 0.042 and ρ = 0.34, p = 0.003, respectivley). No intercorrelation was observed between 25(OH)D, parathormone, cTCa, and iCa^{++} either on D1 or on D7.

DISCUSSION

This prospective study explored the disruptions in the PCC axis in children with fluid-refractory septic shock in a population with high prevalence of undernutrition, hypo-D, and other micronutrient deficiencies. More than 80% of patients had 25(OH)D levels ≤ 20ng/mL. Non-survivors tended to have lower 25(OH)D levels on D1, which increased sharply by D7. Parathormone levels were more than the upper limit of normal (ULN) in 44% of patients. Non-survivors had parathormone levels more than twice what was observed among survivors. Notably, more non-survivors than survivors had values above the ULN, which remained elevated even on D7. Hypocalcemia was common; the prevalence of ionized hypocalcemia was higher than that of total hypocalcemia. cTCa levels increased over the first 10 days in survivors, whereas they decreased in non-survivors. iCa^{++}, however, did not show this divergent trajectory. 25(OH)D and calcium levels on D1 were negatively correlated with illness severity scores and resuscitative requirements, respectively. Parathormone levels were positively correlated with illness severity indicators and negatively correlated with outcome measures.

25(OH)D is stored in adipose tissue and maintains a dynamic equilibrium with its serum level. Its release from adipose tissues and conversion to calcitriol depend on the relative concentrations in these two compartments, metabolic demand, stress hormones, pathophysiological signals, and feedback mechanisms [32]. Sepsis is associated with an increase in 25(OH)D levels in children (sepsis; 74.0 ± 8.1ng/mL *versus* controls; 28.0 ± 12.0ng/mL), which fell significantly after 3 days of antibiotics (44.0 ± 5.3ng/mL) [33]. In another study, hospitalized patients (n = 92)— the majority with infections— reported a

significant fall in 25(OH)D levels after a stormy hospital course (at admission; 71.87 ± 27.25nmol/L *versus* at discharge; 49.03 + 22.25nmol/L) [34]. Sepsis-induced increases in 25(OH)D levels and VDR expression in immune cells support mucosal barrier and antimicrobial functions, modulate adaptive immunity, and counter-regulate the inflammatory cascade [32, 33]. On the other hand, pro-inflammatory cytokines stimulate bone resorption as an immediate response to infection to increase extracellular calcium concentration around the infected site. Higher local calcium concentration, coupled with cytokine-induced increases in CaSR expression on monocytes and macrophages, attracts these cells to the infected site. Chemotaxis and calcium deposition at the infected site further amplify the inflammatory response. To counter-regulate calcium-mediated inflammation, cytokines (e.g., IL-1, IL-6, and TNF) increase CaSR expression in parathyroid chief cells, thyroid C-cells, and renal tubular cells, thereby decreasing parathormone and calcitriol levels and, consequently, serum calcium levels [13, 35]. Prolonged inflammation, however, may increase parathormone secretion, possibly mediated by IL-8 [13]. Genetic expression and activity of CaSRs and VDRs are interdependent and require adequate levels of 25(OH)D to exert their effects.

Prevalence and severity of hypo-D are reported to be high in children from LMICs, which worsens during sepsis [6, 19]. Hypo-D is associated with community-acquired infections [36–38], healthcare-associated infections [11, 39], neonatal sepsis [40], culture-positive sepsis [41], and late-onset sepsis among preterm neonates [42]. Its association with higher illness severity, presence of acute lung injury, need for inotropic and ventilatory support, late shock reversal, prolonged ICU stay, and higher mortality is in agreement with our findings [6, 15, 19–23, 34, 41]. A meta-analysis of 27 pediatric studies (n = 4682) revealed longer duration of ventilation and hospital stay in children with 25(OH)D < 30ng/mL. Further, a subgroup of children with 25(OH)D < 20 ng/mL required more inotropic support than in those with higher levels [43]. The studied patients had a relatively severe degree of systemic inflammation, as evidenced by high PRISM-III and VIS scores, and the need for ventilation in the majority. With a reported positive linear correlation between inflammatory markers and 25(OH)D levels [33], the observed 25(OH)D levels on D1 (≤ 20ng/mL in > 80% and ≤ 5.1ng/mL in 25% of patients) suggest extremely poor stores. Such high severity of pre-existing hypo-D might have precluded any further differentiation between survivors and non-survivors.

Synthesis of the preceding evidence suggests (i) children with hypo-D are predisposed to infections, (ii) once children with pre-existing hypo-D get infected, they fail to release the required amount of 25(OH)D from stores and convert it to calcitriol, and (iii) consequent defective immune modulation of systemic inflammation. This in turn contributes to (a) unabated inflammation, (b) higher illness severity, (c) increased potential of multiorgan dysfunction, and (d) death [16]. Among patients alive during the first week but who died subsequently, continued low levels of 25(OH)D have been reported [15, 44]. In contrast, however, the similar subgroup of patients in the current study had a paradoxical sharp rise on D7. It may suggest a dysregulated cytokine storm, and may require further exploration to determine whether these two groups of patients with pre-existing hypo-D represent distinct biological entities. 25(OH)D levels below 6–12 ng/mL and 20 ng/mL were shown to predict mortality among adults and children, respectively [43, 44–46]. We did not find any such cut-off value.

Cytokines suppress parathormone levels during the initial stages of sepsis in experimental models without pre-existing hypo-D, and then increase them after 24 hours [13, 47]. Clinical data from HICs revealed a similar pattern—lower parathormone levels with new-onset sepsis (enrolled within 48 hours of sepsis diagnosis) [14], while higher levels in those with established sepsis and sepsis-associated multiorgan failure [15, 17, 48]. Both happened with remarkably lower levels of 25(OH)D at admission, and were associated with higher mortality [14, 17]. Studies with higher median 25(OH)D levels and less severe illness reported lower median parathormone levels [19, 40]. However, studies from LMICs, including the current one— with a high prevalence of hypo-D— universally reported elevated parathormone levels in sepsis patients; levels as high as > 10 times the ULN have been observed [44, 45, 49–51]. Early changes might have been missed due to late patient referrals in studies from LMICs. Positive correlations of parathormone levels with illness severity indicators and resuscitative requirements, negative correlations with clinical outcomes including mortality, and persistence of high levels in non-survivors are similar to previously reported observations [23, 44, 50, 52]. The cut-off level to predict mortality was lower in the current study than what is reported in adults with a high prevalence of hypo-D [44, 45]. Pre-existing hypo-D, prolonged and dysregulated systemic inflammation with a predominance of IL-8, and inappropriate falls in calcitriol levels secondary to dysregulated CaSR expression are possible explanations for the presence, severity, and persistence of sepsis-induced secondary hyperparathyroidism [13, 17, 49].

Hypocalcemia is common in sepsis and is caused by a metabolic cascade coordinated by VDR and CaSR. The cascade is characterized by intracellular calcium mobilization, relative hypoparathyroidism, 1-α-hydroxylase deficiency, and cellular resistance to VitD and parathormone [35, 53]. More children had ionized hypocalcemia than total hypocalcemia (60% vs 30%), contrary to previous reports [49]. Higher incidence of hypocalcemia among non-survivors, negative correlation of calcium levels with resuscitative requirements, and positive correlation with IFH_{120} are reported previously as well [23, 49, 50, 52]. Temporal progression of cTCa revealed divergent trajectories—progressive normalization in survivors, while a continued decline in non-survivors. Although a larger sample may be required to negate the lack of significant difference in iCa^{++} levels, findings may indicate effectiveness of compensatory mechanisms in maintaining physiologically active iCa^{++} despite low levels of cTCa, hypo-D, and possible calcipenia. It highlights the importance of measuring both iCa^{++} and cTCa in critically ill patients. Hypocalcemia seems to be an essential accompaniment of systemic inflammation, and a surrogate marker of illness severity rather than a contributor. Calcium replacement has rather worsened inflammation, cellular death, and MODS [53]. Thus, persistent low levels in non-survivors may simply reflect ongoing inflammation and a poor prognosis. However, it is not known if this '*not-a-contributor, but-a-marker*' hypothesis holds for children with severe hypocalcemia (cTCa, ≤ 8.0mg/dL; iCa^{++}, < 0.8mMol/L), severe hypo-D and calcipenia. The latter ones may lead to exaggerated hypocalcemia during sepsis. Generation of more evidence is recommended on the role of hypocalcemia and calcium replacement in children with sepsis, especially in regions with a high prevalence of undernutrition and hypo-D [9, 53].

Post-insult SIPCCADs may be time-dependent, but they look chaotic and pervasive. Low levels of 25(OH)D, its paradoxical elevation, and persistent hypocalcemia despite secondary hyperparathyroidism in non-survivors, and the lack of intercorrelations between components of the PCC axis in children with pre-existing hypo-D, further add to this chaos and may reflect a maladaptive response [23, 40, 49, 50]. Further studies with larger samples and stratification by 25(OH)D levels are required to characterise the contribution of these changes to adverse outcomes.

Persistently high mortality in LMICs, stagnating outcomes in HICs, and emerging insights into the metabolic and immunomodulatory effects of VitD have renewed interest in the role of hypo-D and VitD replacement in sepsis [9, 10, 11, 12, 54]. A meta-analysis of 16 trials (n = 2449) and a narrative review of 21 trials revealed a reduction in ventilation and ICU stay, improved illness severity scores, and increased survival in critically ill adults with VitD replacement [55, 56]. A randomised controlled trial (RCT) demonstrated a significant increase in 25(OH)D and calcitriol levels at D3 and D7 in critically ill adults receiving enteral VitD replacement. It translated into a non-significant improvement in 28-day survival. Improvement, however, was statistically significant in a subgroup of patients with 25(OH)D < 12ng/mL; the number needed to treat was 6 [57]. In contrast, enteral high-dose VitD in another RCT did not show improvement in 90-day survival or any other clinical outcome among critically ill adults with hypo-D [58]. However, there is concern about internal validity of the results due to failure to enrol more than 80% of eligible patients and the trial being stopped much earlier than the planned sample size due to futility. The only available pediatric trial on VitD replacement (n = 109) reported a rise in 25(OH)D levels, reductions in inflammatory cytokines, SOFA score, and incidence of shock in hypo-D children with sepsis, with no impact on ventilation duration or mortality [59]. Impact of VitD and calcium replacement is likely to be greater in children with higher prevalence and severity of hypo-D, undernutrition, and calcipenia [9, 11, 16]. Though mortality benefit may be difficult to assess given multiple contributory socio-economic factors, clinically relevant outcomes may be measured in terms of inotrope-free days, ventilator-free days, PICU-free days, and overall reduction in resource utilization. Results from the ongoing phase 3 trials may improve our understanding further [24, 60].

To the best of our knowledge, this is the first and largest prospective study to assess the longitudinal behaviour of 25(OH)D, parathormone, and calcium in a homogeneous group of fluid-refractory pediatric septic shock from a population with a high prevalence and severity of hypo-D. The study highlights the significant disruption in the PCC axis in children with septic shock. Calcium replacement, given at the treating team's discretion, might have underplayed the incidence of ionized hypocalcemia and the association between hypocalcemia and illness severity indicators. Inclusion of apparently healthy controls from among patients' siblings (living in the same household and sharing the same kitchen) and external controls from the general population would have offered a better comparative perspective. Daily and additional evaluation of calcitriol, calcitonin, magnesium, phosphorus, and alkaline phosphatase during septic shock and post-discharge follow-up would further improve understanding. A comprehensive biochemical assessment of factors affecting iCa^{++} (e.g., blood pH, serum proteins, fatty acids, magnesium, and phosphates) may also provide valuable insights into the complexity of the calci-inflammatory network. Dual-Energy X-ray Absorptiometry (DEXA) scan in patients on follow-up, sibling

controls, and external controls would provide comparative information on the prevalence and severity of calcipenia, and may have therapeutic implications.

CONCLUSIONS

Children with fluid-refractory septic shock from an LMIC exhibited profound disruption in the PCC axis, characterized by hypo-D in more than 80% of patients and secondary hyperparathyroidism in 44% of patients, with non-survivors having levels nearly twice the survivors' levels. Parathormone levels continued to remain elevated while 25(OH)D levels revealed a paradoxical rise on D7 among those who ultimately died. Hypocalcemia was common, and non-survivors failed to raise calcium levels despite persistently elevated parathormone levels. Calcium levels were negatively correlated with resuscitation requirements (fluid boluses, VIS). Parathormone levels were positively correlated with illness severity indicators and resuscitation requirements, while negatively correlated with clinical outcomes. Widespread presence of hypo-D limited the prognostic utility of 25(OH)D in the studied clinical setting, while dysregulated secondary hyperparathyroidism seems to emerge as a predictor of mortality at a cut-off level of 53 pg/mL. These targetable metabolic derangements provide a biological rationale and equipoise for RCTs to evaluate the adjunctive role of VitD replacement, with or without targeted calcium replacement, during resuscitation of pediatric septic shock in LMICs with a high prevalence of undernutrition, hypo-D, and possibly calcipenia.

Declarations

AUTHOR CONTRIBUTION STATEMENT

CMP enrolled the patients, executed the study protocol, conducted a literature review, performed statistical analysis, and prepared the first draft of the manuscript. AKB reviewed the literature, conceptualized, planned, and developed the study design, secured financial support, supervised the conduct of the study and statistical analysis, prepared the final draft of the manuscript, and will act as the guarantor. NS supervised the laboratory analysis and interpreted the laboratory data. DD and JM contributed to the development of the study design and reviewed the final draft.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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AI DISCLOSURE

'Grammarly' was used to enhance English, addressing spelling, grammar, punctuation, and syntax. The manuscript was subsequently reviewed and approved by AKB.

DATA AVAILABILITY

The de-identified dataset supporting the conclusions of this article is available from the corresponding author (Prof. Arun Kumar Baranwal, baranwal1970@gmail.com) upon reasonable request for legitimate research purposes. Requests must include a detailed research proposal, verification of institutional affiliation, and, where required, appropriate ethical approval. Data will be shared in standard formats with documentation, subject to conditions that ensure participant confidentiality, data security, and appropriate attribution to the original study.

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Tables

Table 1: Baseline Demographic Characteristics

Characteristics	Total (n=69)	Survivors (n=43)	Non-Survivors (n=26)	p-value
Age (months)	60 (12, 96)	60 (12, 108)	36 (10.5, 78.5)	p=0.18
Age Groups				
6-12 months, n (%)	22 (31.9%)	13 (30.2%)	9 (34.6%)	p=0.14 (≤60 vs >60 months)
13-60 months, n (%)	18 (26.1%)	9 (20.9%)	9 (34.6%)	
>60 months, n (%)	29 (42%)	21 (48.9%)	8 (30.8%)	
Gender (M:F)	39:30	25:18	14:12	p=0.92
Nutritional Status among patients ≤60 months of age (n=40)				
No Undernourishment (WAZ, ≥ -2), n (%)	25 (62.5%)	16 (72.7%)	9 (50.0%)	
Moderate Underweight (WAZ, <-2 to ≥-3), n (%)	10 (25%)	5 (22.7%)	5 (27.8%)	
Severe Underweight (WAZ, <-3), n (%)	5 (12.5%)	1 (4.5%)	4 (22.2%)	--------
Nutritional Status among patients >60 months of age (n=29)				
No Undernourishment (BMI, ≥ -2), n (%)	26 (89.7%)	18 (85.7%)	8 (100%)	
Thin (BMI, < -2 to ≥-3), n (%)	1 (3.4%)	1 (4.8%)	0	
Severely Thin (BMI, <-3), n (%)	2 (6.9%)	2 (9.5%)	0	
Undernourishment (WAZ, <-2 *plus* BMI <-2), n (%)	18 (26.1%)	9 (20.9%)	9 (34.6%)	p=0.21
Duration of illness (days)	5 (4-8)	5 (4-7)	7 (5-10)	**p=0.038**
Referred from a hospital, n (%)	44 (63.8%)	25 (54.3%)	19 (73.1%)	p=0.21
Stay at referring hospital (days)	1.0 (1.0, 2.0)	2 (1, 2.75)	1 (1, 2)	p=0.87

Abbreviations: WAZ, Weight-for-Age Z score; BMI, Body Mass Index.

Values are presented as Median (Interquartile Range) unless specified otherwise.

Table 2: Critical Care Characteristics

Characteristics	Total (n=69)	Survivors (n=43)	Non-Survivors (n=26)	p-value
Admission Characteristics				
PRISM III in PER	16 (13-19)	15 (12-16.5)	17 (15-22.8)	**0.027**
Lactate (mmol/L)	2.5 (1.4-4.2)	2.1 (1.3-4.1)	3 (1.9-4.2)	0.11
Lactate ≤2mmol/L, n (%)	28 (40.6%)	20 (46.5%)	8 (30.8%)	0.19
Lactate >4mmol/L, n (%)	19 (27.9%)	11 (25.5%)	8 (30.7%)	0.62
Serum Albumin (g/dL)	2.2 (1.9-2.7) (n=66)	2.2 (1.9-2.7) (n=42)	2.15 (2.0-2.6) (n=24)	0.57
Hypoalbuminemia, n (%)	63/66 (95.5%)	40/42 (95.2%)	23/24 (95.8%)	1.00
Serum Creatinine (mg/dL)	0.49 (0.3-0.8)	0.49 (0.4-0.8)	0.51 (0.3-0.8)	0.90
PER Stay (hours)	24 (12-24)	24 (12-24)	24 (12-48)	**0.36**
PRISM III in	18 (14-22)	16 (12-23)	21.5 (17-23.8)	**0.01**
pSOFA Score on Day1	10 (9-13)	10 (7-12)	12 (10-13)	**0.041**
Maximum Lactate in first 24 hrs	3.1 (2.1-4.5)	2.4 (1.7-4.3)	3.9 (2.7-5.9)	**0.018**
Lactate >4 in first 24 hrs, n (%)	24 (34.7%)	12 (28%)	12 (46.1%)	0.093
Characteristics of Critical Care Management				
Fluid bolus at 6 hrs (ml/kg)	20 (20-30)	20 (10-25)	20 (20-30)	0.29
Fluid bolus at 24 hrs (ml/kg)	30 (20-40)	30 (20-40)	40 (20-40)	0.27
VIS score at 6 hrs	20 (10-30)	20 (10-30)	27 (10-47.5)	0.18
VIS score at 24 hrs	**30 (20-68)**	**30 (18-44)**	**56 (27-82)**	**0.006**
Maximum VIS score	55 (30-87)	30 (23-60)	88 (62.5-102.5)	**<0.001**
Duration of Vasoactives (hrs)	90 (48-123)	90 (68-120)	76 (25-143)	0.41
Mechanical Ventilation, n (%)	60 (86.9%)	35 (81.4%)	25 (96.2%)	0.14
Duration of Ventilation (hrs)	120 (72-209)	144 (96-216)	96 (48-192)	**0.023**
Shock Reversed, n (%)	46 (66.7%)	42 (97.7%)	4 (15.4%)	**<0.001**
Time to reversal of shock (hrs)	102 (69.50-132)	102 (80.5-132)	69 (28.5-115)	0.36

PER Stay (Hours)	24 (12 -24)	24 (12-24)	24 (22-45)	**0.041**
PICU Stay (days)	7 (3-12)	8 (3.5-13)	6 (1.8-10)	0.62
ACA Stay (days)	8 (4-13)	9 (4-14)	7 (5-11.6)	0.58
Hospital Stay (days)	11 (5.5 -19)	12.5 (7-19)	10 (5.1-14.8)	0.27

Abbreviations: PER, Pediatric Emergency Room; PICU, Pediatric Intensive Care Unit; PIM 2, Pediatric Index of Mortality 2; pSOFA, Pediatric Sequential Organ Failure Assessment; PRISM III, Pediatric Risk of Mortality Score III; VIS, Vasoactive Inotrope Score, ACA, acute care area ((PER and PICU).

Values are presented as Median (Interquartile Range) unless specified otherwise.

Figures

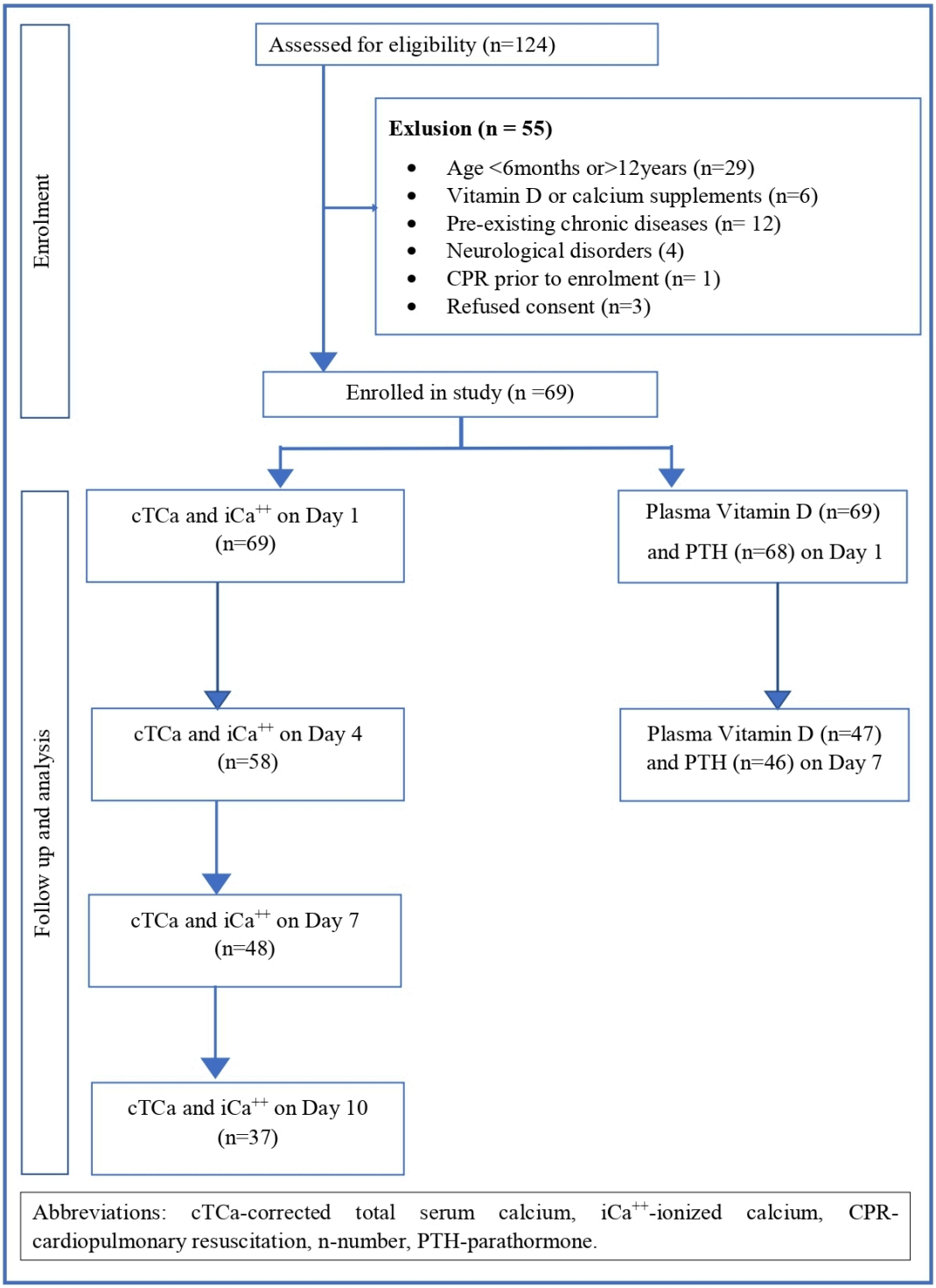


Figure 1

Study flow diagram

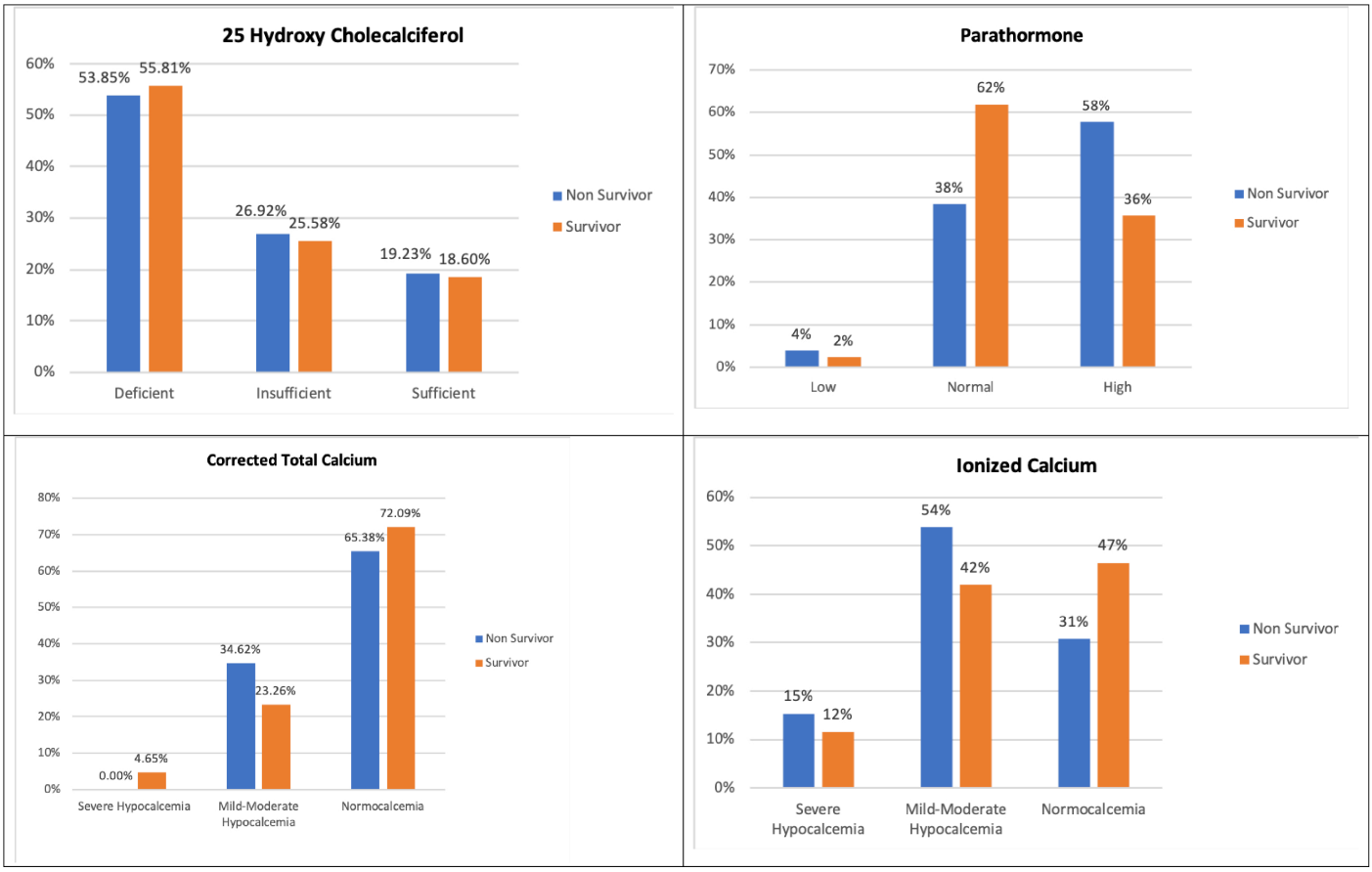


Figure 2

Bar diagrams comparing the distribution of patients across various categories based on serum levels of 25-hydroxycholecalciferol, parathormone, corrected total calcium, and ionized calcium on day 1 between non-survivors and survivors of fluid-refractory septic shock.

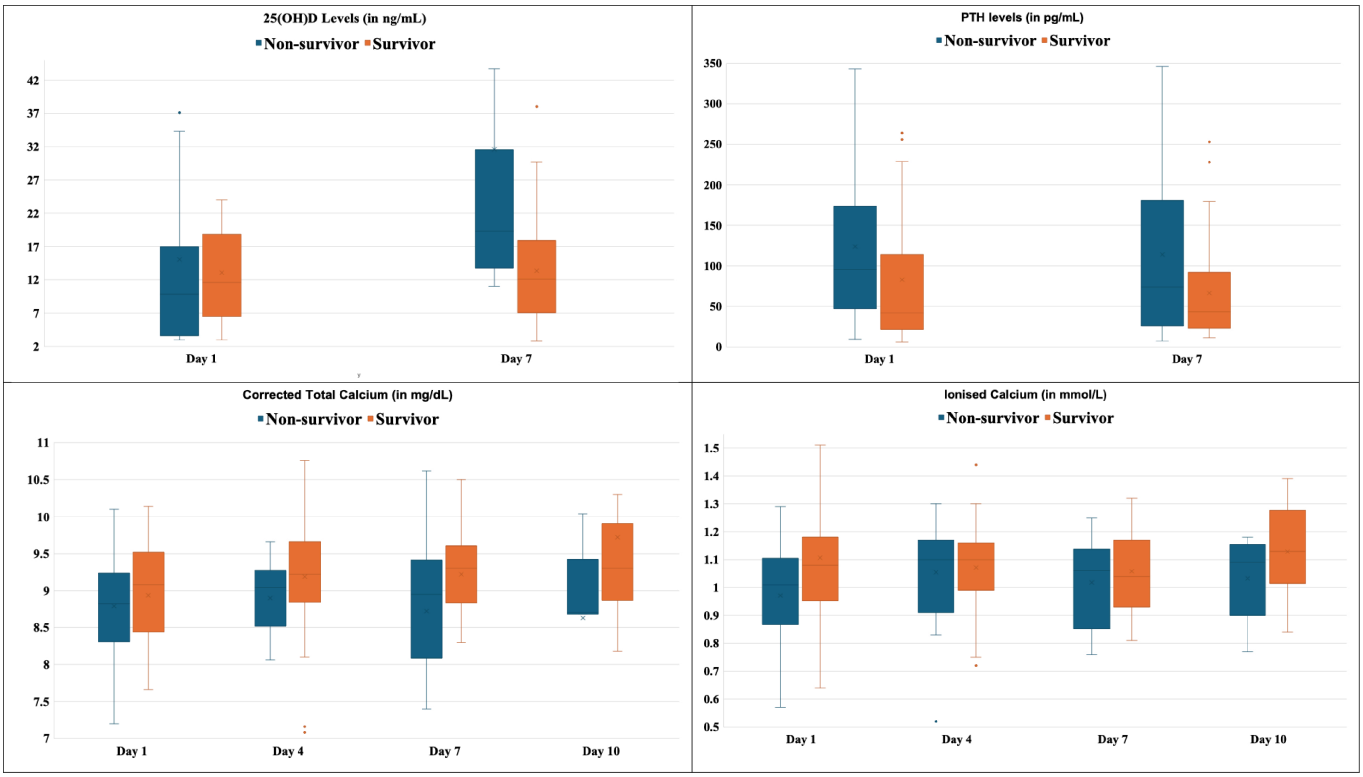


Figure 3

Box-and-whisker plots comparing the trends of 25-hydroxycholecalciferol, parathormone, corrected total calcium, and ionized calcium over the first 10 days between non-survivors and survivors of fluid-refractory septic shock.

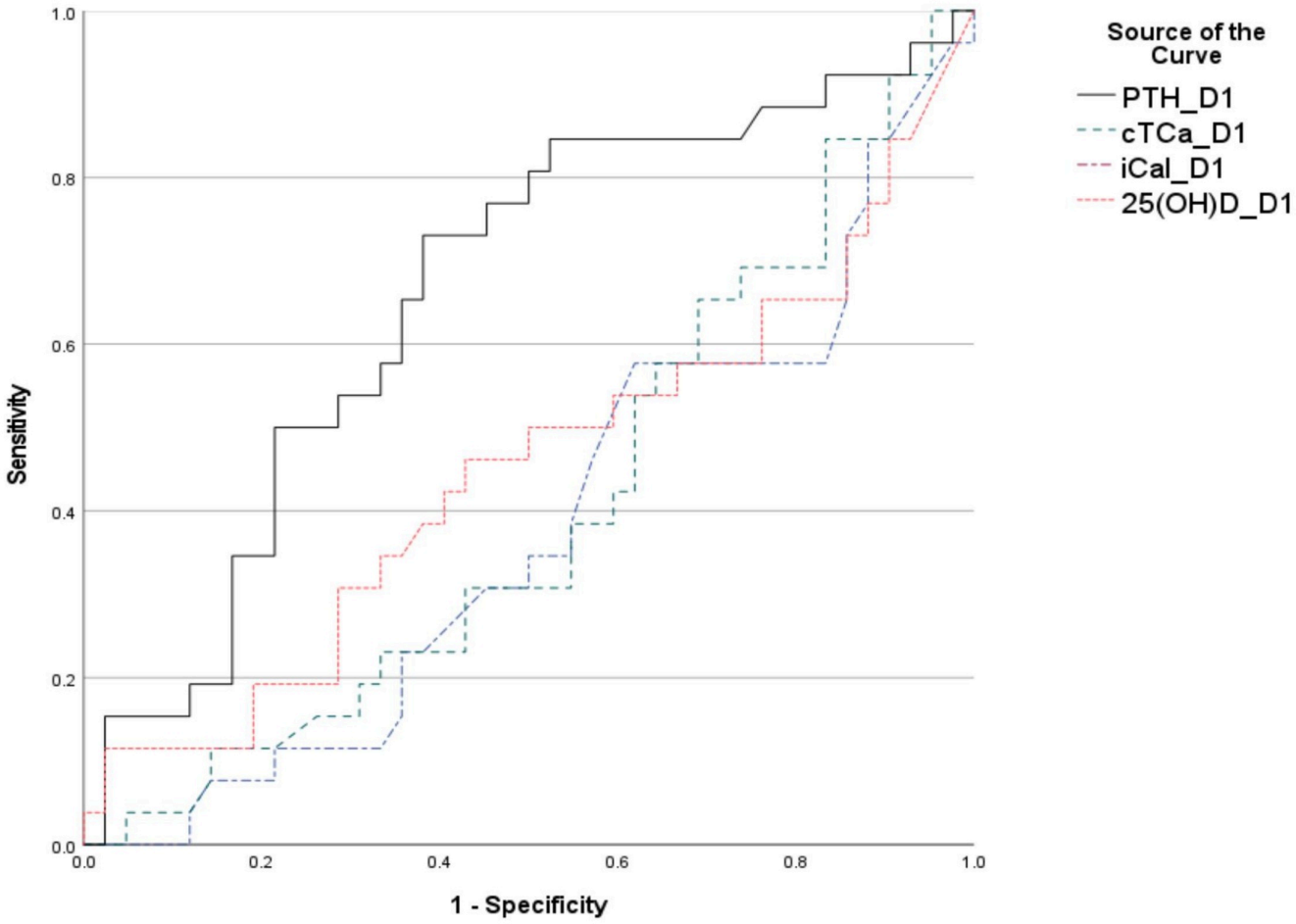


Figure 4

Receiver Operating Characteristic analysis for 25-hydroxycholecalciferol, parathormone, corrected total calcium, and ionized calcium on day 1 to predict mortality in children with fluid-refractory septic shock.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 6.SupplementaryTable1Fig2.docx
- 7.SupplementaryTable2Fig3.docx
- 8.SupplementaryTable3.docx