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ORIGINAL RESEARCH

Shock-Stratified Prognostic Performance of Lactate and Procalcitonin in Pediatric Sepsis In-Hospital Mortality; A Retrospective Cohort Study

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Abstract: **Introduction:** Admission lactate and procalcitonin (PCT) are routinely measured in pediatric sepsis; however, their prognostic performance may vary by clinical phenotype. This study aimed to evaluate the shock-stratified prognostic performance of admission lactate and PCT for predicting in-hospital mortality in children with sepsis.
Methods: In this retrospective cohort study (July 2022 - July 2025), children aged 2 months to 15 years evaluated for suspected sepsis were screened; 193 met eligibility criteria and were included in analyses. Septic shock was recorded at admission, and organ dysfunction was recorded at admission or within the first 24 hours. The Phoenix Sepsis Score was calculated in 143 patients with complete lactate and other required data, whereas the Pediatric Sequential Organ Failure Assessment (pSOFA) score was calculated for all 193 patients using data recorded within the first 24 hours. Admission lactate and PCT were summarized by survival status within shock and non-shock phenotypes. Multivariable logistic regression models adjusted for age and malnutrition assessed biomarker-mortality associations and biomarker × shock interactions. Discrimination was evaluated using shock-stratified receiver operating characteristic (ROC) curves and area under the curve (AUC), with DeLong tests comparing AUCs between phenotypes. **Results:** Among 193 children, 93 (48.2%) had septic shock, 145 (75.1%) had organ dysfunction, and 79 (40.9%) died in hospital. The median Phoenix Sepsis Score was 2.0 (range, 0–12) among 143 patients, while the median pSOFA score was 4.0 (range: 0–21) among all 193 patients. Mortality was higher in shock than non-shock sepsis (66.7% vs 17.0%; odds ratio (OR): 9.77 (95% confidence interval (CI): 4.96-19.24)) and in those with organ dysfunction (53.1% vs 4.2%; OR = 26.03 (95% CI: 6.09-111.34)). Admission lactate was higher in non-survivors than survivors in both non-shock and shock groups ($p<0.05$). In adjusted interaction models, each 1 mmol/L increase in lactate (OR = 1.50, 95% CI: 1.11–2.01; p = 0.0075) and each one-unit increase in natural-log–transformed PCT (ln(PCT)) (OR = 1.34, 95% CI: 1.01-1.79; p=0.0458) were associated with mortality in non-shock sepsis. The lactate × shock interaction (OR = 0.76, 95% CI: 0.55–1.05; p = 0.092) and ln(PCT) × shock interaction (OR = 0.74, 95% CI: 0.52–1.07; p = 0.114) were not statistically significant. Shock-stratified ROC curve analysis showed better discrimination in non-shock than shock for lactate (AUC: 0.76 (95% CI: 0.67-0.85) vs 0.62 (95% CI: 0.40-0.83); DeLong p=0.233) and modest discrimination for natural-log-transformed PCT [ln(PCT)] in both phenotypes (AUC: 0.65 (95% CI: 0.55-0.75) vs 0.61 (95% CI: 0.41-0.80); DeLong p=0.695). **Conclusion:** Admission lactate showed moderate discrimination for in-hospital mortality in non-shock sepsis, whereas discrimination was lower in septic shock. PCT showed modest discrimination across phenotypes. Although AUCs were numerically higher in non-shock sepsis, between-phenotype differences were not statistically significant, supporting phenotype-based interpretation and the need for external validation.

Keywords: Pediatrics; Sepsis; Shock, septic; Lactic acid; Procalcitonin; Biomarkers

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1. Introduction

Pediatric sepsis is a severe medical emergency characterized by rapid progression and remains a major cause of mortality worldwide, with a particularly high disease burden in low- and middle-income countries (1, 2). It was estimated that in 2017 there were approximately 48.9 million cases of sepsis and 11 million sepsis-related deaths, accounting for nearly one-fifth of all global deaths; of these, the Asia-Pacific and Southeast Asia regions bear a disproportionately high burden (3). Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (4). It may progress to septic shock and multiple organ failure if not promptly recognized and managed (5). In critical care practice, lactate and procalcitonin (PCT) are two routinely used

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tests in pediatric patients with suspected or confirmed sepsis (6, 7). Lactate reflects tissue hypoperfusion and metabolic derangements, whereas PCT is a biomarker indicative of bacterial infection and the magnitude of the systemic inflammatory response (7-9). Numerous studies have demonstrated that lactate and/or PCT are associated with disease severity and mortality risk in sepsis (6, 9). However, the prognostic value of these biomarkers may vary according to clinical phenotypes, particularly the presence or absence of septic shock (6, 9). In patients with septic shock, several confounding factors, such as fluid resuscitation, vasopressor use, multiple organ dysfunction, and timing of sample collection may modify the relationship between biomarkers and mortality, leading to heterogeneous predictive performance across different subgroups. In Vietnam, data on pediatric sepsis in intensive care settings remain limited (10, 11). A limited number of studies have evaluated the association between lactate and mortality in children with multiple organ dysfunction syndrome (12); however, few studies have evaluated the shock-stratified prognostic value of lactate and PCT for in-hospital mortality (6, 9). Clarifying this issue has important practical implications for early risk stratification, resource prioritization, and clinical decision-making in the pediatric intensive care unit (PICU). Moreover, most existing studies have focused on individual biomarkers, while the interaction between biomarkers and shock status has not been fully elucidated in real-world clinical practice, particularly in PICUs in middle-income countries such as Vietnam (6, 9-12). This gap limits the ability to individualize monitoring and prognostic strategies for specific pediatric subgroups. Therefore, this study evaluated the shock-stratified prognostic value of admission lactate and PCT for in-hospital mortality in children with sepsis admitted to the PICU. We also examined biomarker–mortality associations using models that included biomarker × shock interaction terms adjusted for age and malnutrition, and summarized key clinical and laboratory characteristics.

2. Methods

2.1. Study design and setting

We conducted a retrospective cohort study at the pediatric intensive care unit (PICU) of Can Tho Children's Hospital, a tertiary pediatric referral center in the Mekong Delta region of Vietnam. Medical records of eligible children admitted between July 2022 and July 2025 were reviewed. Admission lactate and PCT were summarized by survival status within shock and non-shock phenotypes. Multivariable logistic regression models adjusted for age and malnutrition assessed biomarker-mortality associations and biomarker × shock interactions. Discrimination was evaluated using shock-stratified receiver operating characteristic (ROC) curves and area under the curve (AUC), with DeLong tests comparing AUCs between phenotypes.

The study was approved by the Ethics Committee of Can Tho University of Medicine and Pharmacy (Approval code: 22.170.HV/PCT-HĐĐĐ) and authorized by Can Tho Children's Hospital. Patient data were anonymized prior to analysis. The requirement for informed consent was waived in accordance with local ethics regulations for retrospective medical record review. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

2.2. Participants

Children aged 2 months to 15 years were included if they met the pediatric sepsis definition applied in the 2012 Surviving Sepsis Campaign guidelines and based on the International Pediatric Sepsis Consensus Conference criteria. Pediatric sepsis was defined as suspected or confirmed infection accompanied by at least two systemic inflammatory response syndrome (SIRS) criteria, at least one of which was an abnormal core temperature (>38.5°C or <36.0°C) or an abnormal age-specific white blood cell count. The remaining SIRS criteria included age-specific tachycardia, bradycardia in children younger than 1 year, and age-specific tachypnea (13, 14).

Children with pre-existing chronic organ dysfunction prior to the sepsis episode, traumatic brain injury, long-term systemic corticosteroid therapy, coagulation disorders, or hematologic diseases that could substantially alter blood counts (e.g., acute leukemia, bone marrow failure) were excluded.

2.3. Data gathering

Patient selection and cohort formation are summarized in Figure 1. Data were extracted from medical records using a standardized data collection form. Collected variables included demographic characteristics (age and sex), nutritional status (malnutrition, yes/no), and clinical phenotype at admission, including non-shock sepsis or septic shock, suspected focus of infection (respiratory, gastrointestinal, or other), and presence of organ dysfunction (yes/no). The Phoenix Sepsis Score was retrospectively calculated in 143 patients with complete lactate and other required data, whereas the pediatric Sequential Organ Failure Assessment (pSOFA) score was calculated for all 193 patients using clinical and laboratory variables recorded at admission or within the first 24 hours. Admission biomarkers included serum lactate (mmol/L) and procalcitonin (PCT, ng/mL), defined as the first measurements obtained within 6 hours of PICU admission. At our PICU, lactate and PCT were routinely evaluated during the initial evaluation of critically ill children presenting with clinically apparent sepsis or septic shock, before the initiation of sepsis-directed fluid resuscitation, vasoactive support, or antibiotic therapy. In children with a less specific initial presentation, basic clinical and laboratory assessments were performed first, and lactate and PCT were obtained promptly once sepsis was suspected within the first

6 hours. In these patients, biomarker sampling likewise preceded sepsis-directed fluid resuscitation, vasoactive support, and antibiotic administration. Thus, the 6-hour window reflected variation in the timing of clinical recognition of sepsis rather than biomarker collection after treatment. Microbiological data included blood culture results when available. All laboratory tests were performed at the hospital's Department of Laboratory Medicine. Blood biochemistry analyses were conducted using the Hitachi 717 automated analyzer (Hitachi Ltd., Japan), complete blood counts were processed using an automated hematology analyzer, and procalcitonin (PCT) levels were measured using an automated immunoassay system. Venous blood samples were collected under aseptic conditions; samples for complete blood counts were placed in EDTA tubes, whereas samples for biochemical analyses and PCT measurement were collected in serum separator tubes (SST) or heparin tubes in accordance with standard laboratory protocols.

2.4. Definitions

Septic shock was defined according to the 2005 International Pediatric Sepsis Consensus Conference criteria, supported by the 2012 Surviving Sepsis Campaign guidelines, as sepsis accompanied by cardiovascular dysfunction requiring vasoactive support and/or persistent signs of hypoperfusion despite adequate fluid resuscitation (13, 14). For the present analysis, septic shock was operationally defined as the initiation of any continuous vasoactive infusion for sepsis-associated cardiovascular dysfunction within the first 24 hours of PICU admission. Organ dysfunction was defined according to the International Pediatric Sepsis Consensus Conference criteria as dysfunction of at least one organ system documented at admission or within the first 24 hours of PICU stay (14).

2.5. Outcomes

The primary outcome was in-hospital mortality, while the secondary outcome was 24-hour mortality, defined as death occurring within 24 hours of admission. Patients discharged against medical advice in critical condition were classified as treatment failure and counted as non-survivors in the primary outcome analysis; a sensitivity analysis was additionally performed in which these cases were treated as survivors.

2.6. Statistical analysis

Statistical analyses were performed using SPSS (version 26.0) and R (version 4.2.2). Categorical variables were reported as counts and percentages, and continuous variables as medians with interquartile ranges (IQR) due to skewed distributions. Group comparisons were conducted using the Chi-square or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. A two-sided p-value < 0.05 was considered statistically significant. Missing data were handled using a complete-case analysis for each biomarker, and the number of patients with available lactate and procalcitonin (PCT) measurements was reported in the study flowchart in Figure 1. To evaluate whether associations between biomarkers and mortality differed by shock phenotype, multivariable logistic regression models were fitted with in-hospital mortality as the dependent variable. Models included shock status, the biomarker (lactate as a continuous variable and PCT log-transformed as ln(PCT)), and an interaction term between biomarker and shock status, with adjustment for age and malnutrition. Covariates were selected a priori based on clinical relevance. Continuous predictors were mean-centered to improve interpretability. Receiver operating characteristic (ROC) curves were generated for lactate and ln(PCT) to predict in-hospital mortality separately in non-shock and shock phenotypes. Discriminative performance was quantified using the area under the curve (AUC) with 95% confidence intervals (CI). AUCs between phenotypes were compared using DeLong's test (pROC package, R). ROC curves were plotted in R. Only biomarker measurements obtained within 6 hours of PICU admission were eligible for analysis. Sensitivity analysis was performed by reclassifying patients discharged against medical advice in critical condition as survivors.

3. Results

3.1. Baseline characteristics of studied patients

During the study period from July 2022 to July 2025, a total of 193 children with sepsis were included in the analysis. Of these, 93 patients (48.2%) met the criteria for septic shock, while 100 patients (51.8%) were classified as non-shock sepsis, as shown in Figure 1. Baseline clinical characteristics and outcomes of the study population are shown in Table 1. The median age was 42.0 (IQR: 10.5-108.0) months, and 62.7% were male. Malnutrition was documented in 18.7% of cases. Nearly half of the cohort presented with septic shock (48.2%), and organ dysfunction was documented in 75.1% of patients at admission or within the first 24 hours. The cohort represented a critically ill pediatric population with a high rate of septic shock and organ dysfunction. Overall, in-hospital mortality was 40.9%. The median Phoenix Sepsis Score was 2.0 (range, 0–12) among 143 patients, whereas the median pSOFA score was 4.0 (range, 0–21) among all 193 patients (Table 1).

3.2. Mortality by shock phenotype and organ dysfunction

In univariate analysis, both shock phenotype and organ dysfunction were strongly associated with in-hospital mortality (Table 2). Mortality was significantly higher among patients with septic shock compared with those without shock (66.7% vs. 17.0%; OR = 9.77; 95% CI: 4.96–19.24; p < 0.001). Similarly, patients with organ dysfunction exhibited a markedly higher mortality than those without organ dysfunction (53.1% vs. 4.2%; OR = 26.03; 95% CI: 6.09–111.34; p < 0.001).

3.3. Admission PCT and lactate by mortality and shock phenotype

Admission PCT and lactate levels by mortality and shock phenotype are presented in Table 3. Among patients without shock, non-survivors had significantly higher admission lactate levels than survivors (median 3.06 mmol/L (IQR: 2.33–7.66) vs. 2.33 mmol/L (IQR: 1.60–3.43); p = 0.041), whereas PCT levels did not differ significantly between groups (25.10 ng/mL (IQR: 1.49–80.54) vs. 1.48 ng/mL (IQR: 0.44–23.02); p = 0.055). Similarly, among patients with septic shock, non-survivors exhibited higher lactate concentrations compared with survivors (6.00 mmol/L (IQR: 3.66–11.20) vs. 3.85 mmol/L (IQR: 2.58–6.52); p = 0.028), while PCT levels were comparable between the two groups (25.05 ng/mL (IQR: 9.98–59.87) vs. 51.71 ng/mL (IQR: 2.01–91.69); p = 0.558).

3.4. Multivariable interaction models of in-hospital mortality

Multivariable interaction models for in-hospital mortality are presented in Table 4. Septic shock was independently associated with in-hospital mortality in both models (lactate model: OR = 4.02; 95% CI: 1.59–10.19; p = 0.0033; ln(PCT) model: OR = 8.34; 95% CI: 3.86–17.98; p < 0.001). Among patients without shock, higher lactate levels (OR = 1.50 per 1 mmol/L; 95% CI: 1.11–2.01; p = 0.0075) and higher ln(PCT) levels (OR = 1.34; 95% CI: 1.01–1.79; p = 0.0458) were associated with increased mortality. In contrast, interaction terms between biomarkers and shock were not statistically significant (lactate × shock: OR = 0.76; 95% CI: 0.55–1.05; p = 0.092; ln(PCT) × shock: OR = 0.74; 95% CI: 0.52–1.07; p = 0.114). Age and malnutrition were not independently associated with in-hospital mortality (all p > 0.05).

3.5. ROC curve analysis stratified by shock phenotype

Results of the phenotype-stratified ROC analysis are presented in Table 5. In the non-shock group, lactate demonstrated better discrimination for in-hospital mortality than ln(PCT), with an AUC of 0.76 (95% CI: 0.67–0.85) compared with 0.65 (95% CI: 0.55–0.75), as illustrated in Figure 2. In contrast, in the shock phenotype, the discriminative performance of both biomarkers was attenuated, with an AUC of 0.62 (95% CI: 0.40–0.83) for lactate and 0.61 (95% CI: 0.41–0.80) for ln(PCT), as shown in Figure 2. Comparison of AUCs between phenotypes using the DeLong test revealed no statistically significant differences for ln(PCT) (p = 0.695) or lactate (p = 0.233); the wider confidence intervals observed in the shock group reflect greater uncertainty in these estimates within this population.

4. Discussion

This study yielded three main findings. First, septic shock and organ dysfunction were strongly associated with in-hospital mortality in children with sepsis. Second, higher admission lactate and natural-log-transformed procalcitonin (ln(PCT)) levels were independently associated with mortality among children with non-shock sepsis, although the biomarker × shock interaction terms were not statistically significant. Third, admission lactate showed moderate discrimination for mortality in non-shock sepsis, whereas the discriminative performance of both lactate and ln(PCT) was numerically lower in septic shock; however, the between-phenotype differences in AUC were not statistically significant. These findings support interpreting admission biomarkers within the patient's hemodynamic phenotype rather than using them as standalone prognostic tools.

In our study, the pediatric sepsis population admitted to the PICU exhibited a high severity of illness, as reflected by a septic shock rate approaching 50% and organ dysfunction present in up to 75% of patients. A similarly high burden of organ dysfunction has been reported in other PICU populations, with multiple organ dysfunction documented in more than 70% of critically ill children in one cohort (15). This underscores the substantial disease burden in our cohort and supports its suitability for evaluating prognostic biomarkers. Among 143 patients with available Phoenix Sepsis Score data, the median score was 2.0 (range, 0–12), corresponding to the proposed threshold for potentially life-threatening infection-associated organ dysfunction, while the broad range demonstrated substantial heterogeneity in disease severity (2). Among all 193 patients, the median pSOFA score was 4.0 (range: 0–21), similarly indicating varying degrees of multiorgan dysfunction, consistent with PICU evidence linking a greater burden of organ dysfunction and higher severity scores to increased mortality (15). These findings support the complementary use of severity scores, shock status, and biomarkers to characterize clinical severity. The in-hospital mortality rate in our study was approximately 41%, markedly higher than that reported in many international cohorts. For example, a study from South America reported a sepsis-related mortality of 14.2% among critically ill children (16), while a multicenter retrospective study across nine PICUs in three Asian countries reported a PICU mortality of 19.2% (17). This difference may be partly explained by the high prevalence of septic shock and organ dysfunction in our cohort, as well as potential differences in case mix and healthcare resources. Importantly, the high mortality rate provided an adequate number of outcome events to allow robust assessment of prognostic biomarkers. Given this severe clinical profile, our cohort is particularly appropriate for investigating biomarkers associated with systemic inflammation and tissue hypoperfusion. Lactate is a well-established indicator of impaired tissue perfusion and has been consistently associated with mortality in pediatric sepsis (6, 8), whereas procalcitonin reflects the intensity of the inflammatory response and severity of bacterial infection (7, 9). Evaluating these biomarkers in a high-risk PICU population may therefore offer clinically relevant insights for early risk

stratification and therapeutic decision-making. Our study demonstrates that septic shock and organ dysfunction are decisive determinants of in-hospital mortality in children with severe sepsis. Mortality among patients with septic shock reached 66.7%, compared with 17.0% in those without shock, indicating that the development of shock represents a critical prognostic turning point associated with markedly adverse outcomes. This finding is consistent with previous PICU-based evidence showing substantial mortality among children with severe sepsis and septic shock in Asian settings (17). Similarly, organ dysfunction was strongly associated with mortality. Patients with organ dysfunction had a mortality rate of 53.1%, compared with only 4.2% among those without organ dysfunction, highlighting the profound impact of multiorgan involvement on outcomes. This finding is consistent with previous PICU studies reporting a high mortality burden among children with multiple organ dysfunction syndrome (15). Collectively, evidence from retrospective and longitudinal studies consistently demonstrates that mortality risk increases with the number of failing organs, underscoring multiple organ dysfunction syndrome (MODS) as a central pathophysiological driver of death in pediatric sepsis. Our findings reinforce the importance of early and comprehensive assessment of shock and organ dysfunction in the PICU, as these features identify a subgroup of patients at particularly high risk who may benefit from intensified monitoring and timely therapeutic interventions. Admission lactate levels were significantly higher in non-survivors than in survivors in both non-shock patients and those with septic shock, supporting the role of lactate as a prognostic marker across different stages of disease severity. This finding reinforces the concept that lactate reflects an imbalance between tissue oxygen supply and demand due to impaired perfusion, not only during overt shock but also in earlier phases of sepsis before shock becomes clinically apparent (8). Consistent with this interpretation, previous retrospective studies and clinical trials have demonstrated that persistently elevated lactate levels are independently associated with increased mortality risk in sepsis, even after initial resuscitation efforts (18). In contrast, procalcitonin (PCT) showed only a borderline difference between survivors and non-survivors in the non-shock group and no significant association with mortality among patients with septic shock. This suggests that a single admission PCT measurement may have limited prognostic utility in advanced sepsis, where immune dysregulation, heightened inflammatory responses, and early antibiotic administration can lead to substantial variability in PCT concentrations (7). Recent studies have similarly reported that while PCT is valuable for identifying bacterial infection, its prognostic performance in severe septic shock is suboptimal when based on a single time-point assessment and should be interpreted alongside other biomarkers or clinical severity indices (19). Taken together, our findings indicate that in a cohort of children with severe sepsis encompassing both shock and non-shock phenotypes, lactate represents a more consistent and reliable biomarker for early mortality risk stratification. In contrast, PCT may provide complementary prognostic information when integrated with other clinical variables or evaluated longitudinally rather than in isolation.

In this study, lactate and ln-transformed procalcitonin (ln(PCT)) levels measured within the first 6 hours of admission demonstrated independent prognostic value for mortality or disease progression in children with sepsis, with their predictive performance varying according to shock status. In the non-shock subgroup, both lactate and ln(PCT) showed significant positive associations with the risk of adverse outcomes, whereas in patients with septic shock, their prognostic performance was attenuated, suggesting the contribution of additional pathophysiological mechanisms beyond isolated tissue hypoperfusion. These findings have important clinical implications, as they indicate that biomarker interpretation should be contextualized within the patient's hemodynamic phenotype. Although lactate is traditionally considered a marker of impaired tissue perfusion, in pediatric septic shock elevated lactate levels may also reflect β-adrenergic stimulation, mitochondrial dysfunction, and impaired hepatic and renal clearance (8, 20). This may explain why, in our models, the odds ratios for lactate and ln(PCT) were lower in the shock subgroup than in the non-shock subgroup. Similarly, while PCT reflects the magnitude of the systemic inflammatory response, once shock has developed, prognosis is more strongly driven by the severity of multiple organ dysfunction and the response to therapy rather than by the absolute baseline biomarker levels. Our results are consistent with and extend previous evidence. A study by Uppala (2025) in pediatric sepsis reported that baseline PCT levels were not predictive of mortality, whereas PCT kinetics and 24-hour clearance had strong prognostic value (21). Several other studies have likewise demonstrated that the prognostic performance of single time-point PCT measurements is inferior to that of dynamic PCT monitoring over time (9, 22, 23). This aligns with our observation that isolated ln(PCT) values are only clinically meaningful when interpreted within a specific clinical context, particularly shock status. Regarding lactate, an analysis of a Pediatric Intensive Care (PIC) database including 288 children with sepsis identified a nonlinear association between lactate levels and 28-day mortality, with a threshold of 2.2 mmol/L (24). Scott et al. (2017) reported that a lactate level >36 mg/dL had high specificity (92.3%) but low sensitivity (20.0%) for predicting mortality (6). In our cohort, we similarly observed a graded increase in risk associated with rising lactate levels in the non-shock group, further supporting the role of lactate as an early prognostic marker prior to the development of overt hemodynamic instability. However, our findings should not be interpreted as evidence negating the prognostic value of biomarkers in children with septic shock. The lack of statistically significant interaction between biomarkers and shock status may be attributable to limited sample size, although the direction of effect remains

biologically consistent. Another plausible explanation is that during the shock phase, aggressive therapeutic interventions such as vasoactive support, mechanical ventilation, and fluid resuscitation may attenuate or "dilute" the association between baseline biomarker levels and outcomes, whereas in non-shock patients, biomarkers may more accurately reflect the underlying disease burden. From a practical perspective, our results suggest that lactate and PCT should not be used as standalone prognostic tools, but rather interpreted in conjunction with hemodynamic status and the degree of organ dysfunction. In children without shock, elevated lactate or ln(PCT) levels may aid in the early identification of high-risk patients who require closer monitoring and timely optimization of therapy. Conversely, in children already requiring vasoactive support, strategies focusing on biomarker kinetics and trends over time, together with other indices of tissue perfusion, may be more informative than reliance on absolute admission values alone.

This study demonstrated that lactate tended to have superior discriminative performance compared with procalcitonin in children with non-shock sepsis (AUC: 0.76 vs. 0.65), whereas in the shock subgroup, the performance of both biomarkers declined and no statistically significant difference was observed. These findings suggest that the predictive value of biomarkers is highly dependent on hemodynamic phenotype, and that applying a single universal cutoff across all sepsis patients may be inappropriate. These results have important practical implications, as lactate and PCT are currently often used as risk assessment markers relatively independent of clinical context. Lactate reflects tissue hypoperfusion and cellular metabolic derangements; therefore, its better performance in the pre-shock stage is pathophysiologically plausible. In contrast, during established shock, lactate levels are influenced by multiple factors including vasoactive medications, hepatic and renal dysfunction, and lactate-containing fluids which may weaken the association between lactate concentration and prognosis. PCT primarily reflects the magnitude of the bacterial inflammatory response, and thus its ability to predict mortality is more limited, particularly when impaired perfusion becomes the dominant pathophysiological mechanism. Our findings are partially consistent with recent studies identifying lactate as a prognostic marker for mortality in pediatric sepsis. Data from a pediatric intensive care database indicate that in children with sepsis, each 1 mmol/L increase in lactate is associated with a significant increase in mortality risk, and that lactate levels ≥2.2 mmol/L are linked to a substantially higher 28-day mortality risk (hazard ratio (HR) = 3.61; 95% CI: 1.24–10.54) (24). Additionally, another study involving 149 pediatric patients reported that lactate measured at 6 hours after admission achieved an AUC of 0.83 for mortality prediction, whereas admission lactate had more limited prognostic value (25). These findings further support the concept that lactate shows a strong association with adverse outcomes, particularly when assessed after initial resuscitation. Regarding procalcitonin, a study by Raúl Bustos B. (2015) reported that PCT measured at PICU admission demonstrated good prognostic performance for mortality, with an AUC of 0.80 (95% CI: 0.69–0.88), and excellent performance for predicting septic shock, with an AUC of 0.91, outperforming lactate (26). However, such results are often observed in studies with different designs and patient populations (e.g., more homogeneous disease severity or a predominance of severe shock), which may lead to higher discriminative performance compared with our observations, where ln(PCT) achieved relatively low AUC values across both hemodynamic phenotypes. The marked difference in lactate performance between non-shock and shock subgroups in our study is also consistent with reports emphasizing the importance of lactate kinetics rather than single static measurements (27, 28). This may explain why, in the context of septic shock, where tissue hypoperfusion and the effects of resuscitative interventions are more complex, a single admission lactate value has limited ability to predict mortality without accounting for temporal changes. Conversely, studies incorporating composite indices or clinical severity scores (such as pSOFA) generally achieve higher prognostic performance than lactate or PCT alone, highlighting the necessity of integrating multiple clinical and biological factors to optimize risk stratification in sepsis. Overall, our findings are concordant with the existing literature in demonstrating an association between lactate and mortality in pediatric sepsis; however, differences in study design, timing of biomarker sampling, and patient stratification by phenotype may substantially influence AUC estimates and the apparent prognostic value of individual biomarkers. Importantly, most prior studies did not stratify patients by shock status; thus, our findings add evidence that biomarker performance varies according to hemodynamic phenotype and should be interpreted within a specific clinical context. In addition to these interpretations, alternative explanations should be considered. The reduced performance of lactate in the shock subgroup may be related to epinephrine-induced lactate production, impaired lactate clearance in patients with organ failure, or variations in resuscitation protocols, rather than reflecting a limitation of lactate's intrinsic biological relevance. Similarly, PCT levels may be influenced by the timing of sampling and the source of infection. These factors underscore that biomarkers should be regarded as adjunctive tools rather than substitutes for comprehensive clinical assessment. Clinically, admission lactate may aid early risk stratification in non-shock sepsis. In septic shock, single admission lactate or PCT values are unlikely to be sufficient for prognostication and should be interpreted alongside hemodynamic status, tissue-perfusion indices, organ dysfunction, and validated severity scores. Although AUCs were numerically higher in non-shock than shock phenotypes, DeLong tests showed no statistically significant between-phenotype differences. Overall discrimination was moderate, supporting cautious clinical application and the need for external validation.

5. Limitations

This study has several limitations that should be acknowledged. First, the retrospective, single-center design limits causal inference and reduces the generalizability of the findings. As a tertiary referral PICU in a middle-income country, our center is likely to receive a high proportion of critically ill children, which may partly explain the relatively high in-hospital mortality observed in this cohort. Second, although the sample size was sufficient to detect associations between admission lactate, procalcitonin, and in-hospital mortality, the study may have been underpowered to identify statistically significant interactions between biomarkers and shock status. The wide confidence intervals and nonsignificant interaction terms suggest that larger, multicenter studies are needed to more robustly evaluate effect modification by hemodynamic phenotype. Third, biomarker measurements were limited to a single early time point within the first 6 hours of PICU admission. Although lactate and PCT sampling preceded sepsis-directed fluid resuscitation, vasoactive support, and antibiotic therapy in all patients, the interval between PICU admission and biomarker measurement varied according to the timing of sepsis recognition. This temporal variation may have introduced some variability in the measured lactate and PCT concentrations. Dynamic parameters such as lactate clearance or procalcitonin kinetics, which may provide additional prognostic information, particularly in children with septic shock, were not assessed. Fourth, although multivariable models were adjusted for age and nutritional status, residual confounding cannot be fully excluded. Important clinical factors, including overall disease severity, resuscitation strategies, vasoactive drug use, and organ support modalities, were not incorporated into the models. Finally, the study focused solely on in-hospital mortality and did not evaluate longer-term outcomes such as PICU length of stay or post-discharge functional status. Despite these limitations, this study provides real-world evidence supporting the prognostic value of lactate and procalcitonin when interpreted according to hemodynamic phenotype. Our findings underscore the need for prospective, multicenter studies with larger sample sizes that integrate biomarker kinetics and standardized clinical severity scores to better inform risk stratification in pediatric sepsis.

6. Conclusions

In children with non-shock sepsis, admission lactate may support early risk stratification, whereas discrimination was lower in septic shock. These findings suggest that lactate and PCT should be interpreted within the hemodynamic context and alongside organ dysfunction rather than used as standalone prognostic tests. Larger, multicenter studies incorporating biomarker kinetics and standardized severity measures are needed to externally validate phenotype-stratified performance and to inform clinically useful thresholds in pediatric sepsis.

7. Declarations

7.1. Acknowledgments

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The authors declare that the study received no funding.

7.3. Author Contributions

Conceptualization: VVT, LTD
Study design: VVT, TMD
Data collection: VVT, TMD
Data management: VVT, LTD
Statistical analysis: VVT
Supervision: TMD
Manuscript drafting: VVT, LTD
Manuscript revision: All authors
All authors read and approved the final manuscript.

7.4. Conflict of Interest

The authors declare no conflict of interest.

7.5. Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

7.6. Using artificial intelligence chatbots

The authors used artificial intelligence chatbots solely for language editing and grammatical refinement. All outputs were reviewed and verified by the authors, who take full responsibility for the final manuscript.

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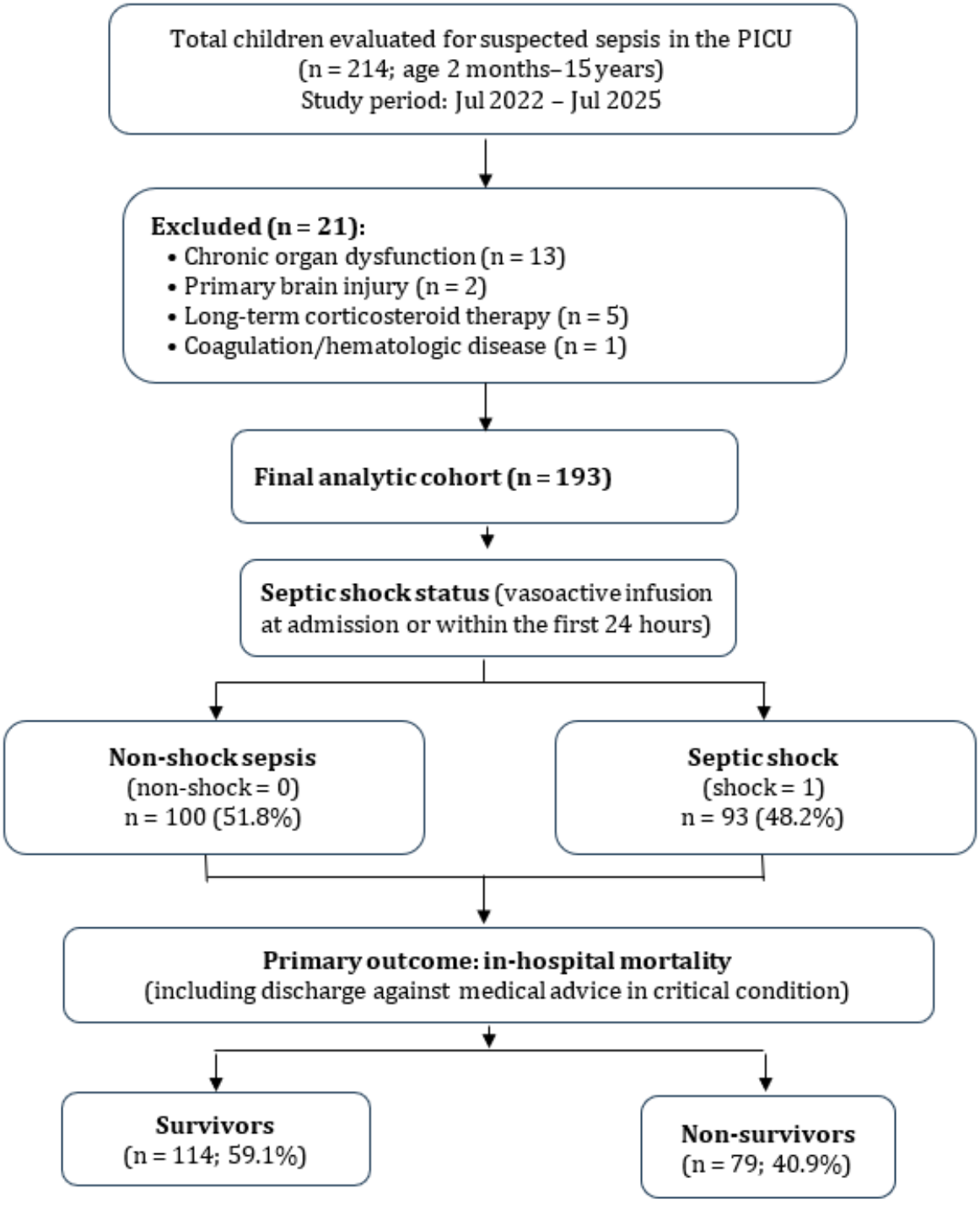

Figure 1: Flowchart of patient selection and study cohort formation. PICU: pediatric intensive care unit.

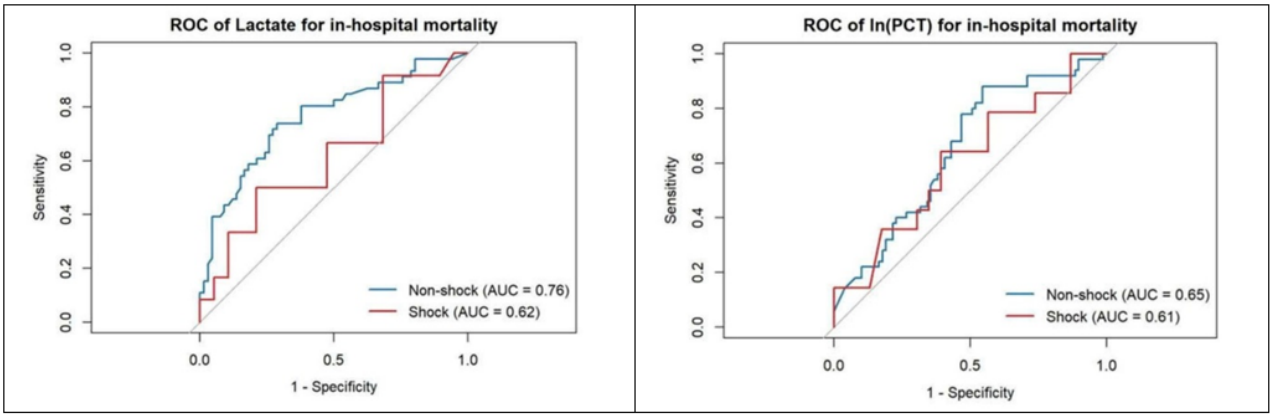

Figure 2: Receiver operating characteristic (ROC) curves of admission lactate and procalcitonin (PCT) for predicting in-hospital mortality, stratified by shock phenotype. AUC: area under the ROC curve; ln(PCT): natural-log–transformed procalcitonin.

Table 1: Baseline clinical characteristics and outcomes of the study population (n = 193)

Variable	Overall
Age, months, median (IQR)	42.0 (10.5-108.0)
Male sex, n (%)	121 (62.7)
Malnutrition, n (%)	36 (18.7)
Septic shock, n (%)	93 (48.2)
Organ dysfunction, n (%)	145 (75.1)
In-hospital mortality, n (%)	79 (40.9)
Phoenix Sepsis Score, median (range)	2.0 (0-12)
pSOFA score, median (range)	4.0 (0-21)

pSOFA: Pediatric Sequential Organ Failure Assessment (pSOFA).

Table 2: In-hospital mortality by shock phenotype and organ dysfunction (n = 193)

Category	Survivors	Non-survivors	Odds ratio	P*
Shock phenotype				
Non-shock (n = 100)	83 (83.0)	17 (17.0)	Reference	<0.001
Septic shock (n = 93)	31 (33.3)	62 (66.7)	9.77 (4.96-19.24)	
Organ dysfunction				
No (n = 48)	46 (95.8)	2 (4.2)	Reference	<0.001
Yes (n = 145)	68 (46.9)	77 (53.1)	26.03 (6.09-111.34)	

Data are presented as number (%). Odds are presented with 95% confidence interval. *P values were calculated using the Chi-square test.

Table 3: Admission procalcitonin and lactate levels by mortality, stratified by shock phenotype

Shock phenotype	Procalcitonin (ng/mL)	P value	Lactate (mmol/L)	P value
Non-shock				
Survivors	1.48 (0.44-23.02)	0.055	2.33 (1.60-3.43)	0.041
Non-survivors	25.10 (1.49-80.54)		3.06 (2.33-7.66)	
Shock				
Survivors	51.71 (2.01-91.69)	0.558	3.85 (2.58-6.52)	0.028
Non-survivors	25.05 (9.98-59.87)		6.00 (3.66-11.20)	

*Values are presented as median (interquartile range). P values were calculated using the Mann-Whitney U test.

Table 4: Multivariable interaction models for in-hospital mortality (adjusted for age and malnutrition)

Variable	Model 1:		Model 2:	
	Lactate × Shock	p	ln(PCT) × Shock	p
Shock	4.02 (1.59-10.19)	0.0033	8.34 (3.86-17.98)	<0.001
Lactate (effect in non-shock)	1.50 (1.11-2.01)	0.0075	—	—
Lactate × Shock	0.76 (0.55-1.05)	0.092	—	—
ln(PCT) (effect in non-shock)	—	—	1.34 (1.01-1.79)	0.0458
ln(PCT) × Shock	—	—	0.74 (0.52-1.07)	0.114
Age	1.00 (0.99-1.00)	0.227	1.00 (0.99-1.01)	0.801
Malnutrition	1.83 (0.67-5.01)	0.241	0.91 (0.34-2.43)	0.846

Data are presented with 95% confidence intervals. *Model 1 includes lactate (continuous, mean-centered), shock status, and their interaction; N = 143. Model 2 includes ln-transformed PCT (mean-centered), shock status, and their interaction; N = 166. Both models adjusted for age and malnutrition. ln(PCT): natural-log–transformed procalcitonin.

Table 5: Phenotype-stratified ROC curve analysis of admission biomarkers for in-hospital mortality

Biomarker	Phenotype	N	AUC (95% CI)	P value*
ln(PCT)	Non-shock	87	0.65 (0.55-0.75)	0.695
	Shock	79	0.61 (0.41-0.80)	
Lactate	Non-shock	70	0.76 (0.67-0.85)	0.233
	Shock	73	0.62 (0.40-0.83)	

* DeLong test compares area under the receiver operating characteristic (ROC) curves (AUCs) between shock and non-shock phenotypes for the same biomarker. ln(PCT): natural-log–transformed procalcitonin; CI: confidence interval.