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Correlating Serum Biomarkers with Clinical Outcomes in Pediatric Sepsis; A Retrospective Observational Study

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ABSTRACT

Introduction: Pediatric sepsis is a major cause of morbidity and mortality worldwide, particularly in resource-limited settings. Early identification of high-risk patients is essential for improving outcomes. Inflammatory biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and interleukin-6 (IL-6) have been studied for their prognostic value, but their correlation with disease severity and mortality in pediatric sepsis remains unclear. ***Aims & Objectives:*** This study aimed to assess the association between serum biomarkers (CRP, ESR, PCT, and IL-6) and clinical outcomes, including Pediatric Intensive Care Unit (PICU) stay, mechanical ventilation, multi-organ dysfunction syndrome (MODS), and in-hospital mortality in children with sepsis. ***Methodology:*** A retrospective observational study was conducted at two tertiary-care hospitals in Karachi, Pakistan, from January to December 2024. A total of 233 pediatric sepsis patients were included. Data on demographics, clinical parameters, biomarker levels, and outcomes were collected. Statistical analyses, including Pearson correlation and logistic regression, were performed to evaluate biomarker predictive value. ***Results & Findings:*** The mean age was 3.7 years (±2.5 SD), with a male predominance (58.8%). Severe malnutrition (28.3%) was common. The average PICU stay was 8.6 days, and 60.9% required mechanical ventilation. The mortality rate was 23.6%. Non-survivors had significantly higher biomarker levels, with IL-6 showing the strongest correlation with severity ($r = 0.68$, $p < 0.001$) and mortality prediction (OR = 2.7, $p < 0.001$). ***Conclusion***: Elevated IL-6, PCT, CRP, and ESR levels are strongly linked to pediatric sepsis severity and mortality, with IL-6 being the most reliable predictor. Biomarker-based risk stratification could improve management strategies, particularly in resource-limited settings. Further prospective studies are needed to validate findings and develop cost-effective rapid biomarker assays.

KEYWORDS: Pediatric sepsis, Inflammatory biomarkers, IL-6, Prognostic indicators, Mortality prediction

INTRODUCTION

Sepsis is a life-threatening condition characterized by a dysregulated systemic inflammatory response triggered by infection. It is a major cause of morbidity and mortality worldwide, particularly in vulnerable populations such as neonates and young children. Pediatric sepsis presents unique diagnostic and management challenges due to the subtle and often non-specific clinical presentation in its early stages. In infants and young children, symptoms such as fever, tachycardia, or respiratory distress can mimic less severe infections, leading to potential delays in diagnosis and intervention [1,2]. This delay is particularly concerning as sepsis can rapidly progress to septic shock and multiorgan dysfunction, significantly increasing the risk of mortality and long-term complications. Early identification and appropriate management are crucial for improving survival outcomes and reducing the burden on healthcare resources [3].

Despite advancements in critical care medicine, pediatric sepsis remains a diagnostic challenge due to the reliance on clinical judgment and conventional laboratory markers, which often lack specificity and sensitivity. Studies have shown that approximately 12% of well-appearing febrile infants may have underlying serious bacterial infections that could progress to sepsis if not promptly diagnosed [4]. Furthermore, the economic burden of sepsis management is substantial, with an estimated annual cost exceeding $20 billion in the United States alone [5]. This highlights the urgent need for reliable diagnostic tools that can facilitate early detection, risk stratification, and targeted therapeutic interventions for pediatric sepsis patients. Biomarkers have gained considerable attention in sepsis research as they offer a potential solution for improving early detection and prognosis prediction. Biomarkers are measurable biological compounds that provide insights into the underlying pathophysiological processes of disease states. In sepsis, biomarkers can reflect systemic inflammation, immune response dysregulation, and organ dysfunction, aiding in disease stratification and outcome prediction [6]. Among the currently available biomarkers, Erythrocyte sedimentation Rate (ESR), C-reactive protein (CRP) and procalcitonin (PCT) are widely used for detecting infection-related inflammation; however, their specificity in differentiating sepsis from other inflammatory conditions remains limited [8,9]. Emerging research suggests that novel inflammatory biomarkers such as interleukin-10 (IL-10), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-alpha (TNF-α) may play a crucial

role in the pathogenesis of sepsis, but their clinical utility remains underexplored [7]. Rather than relying on a single biomarker, a multimodal approach utilizing multiple biomarkers in tandem may provide a more accurate assessment of sepsis severity and prognosis [10].

C-Reactive Protein (CRP): C-reactive protein (CRP) is a widely recognized biomarker for acute inflammation and is extensively studied in the context of sepsis. It is synthesized by the liver in response to interleukin-6 (IL-6), which is produced during the inflammatory response to cellular injury. CRP plays a role in facilitating complement binding to foreign and damaged cells. Compared to other inflammatory markers, such as IL-6 and IL-1, CRP exhibits a delayed elevation during the course of sepsis [11]. The sensitivity of CRP in diagnosing sepsis varies between 44% and 100%, while specificity ranges from 58% to 98%, depending on the cut-off value used. However, CRP is a marker of inflammation rather than infection, leading to its elevation in a range of conditions, including viral infections, malignancies, trauma, post-surgical states, burn injuries, tissue necrosis, immune-mediated inflammatory diseases, crystal-induced inflammatory diseases, and obesity [12].

Erythrocyte Sedimentation Rate (ESR): The erythrocyte sedimentation rate (ESR) is another commonly utilized biomarker for sepsis and serves as a non-specific indicator of tissue injury. ESR has greater diagnostic utility than leukocyte count in identifying inflammatory conditions and differentiating mild versus severe inflammation [8]. It consistently exhibits high sensitivity and specificity for inflammatory diseases and malignancies but has limited efficacy in distinguishing between different causes of inflammation, such as malignancy versus infection. In burn patients, ESR levels are elevated but fail to differentiate between infected and non-infected individuals. ESR is also an ineffective marker for neonatal sepsis due to the low sedimentation rate observed in neonates, which is attributed to high hematocrit levels. Additionally, baseline ESR values tend to be low in individuals with decreased fibrinogen levels, sickle cell disease, polycythemia, or congestive heart failure [5].

Procalcitonin (PCT): Procalcitonin (PCT) has gained significant recognition as a biomarker for sepsis. PCT is a precursor of calcitonin, which is produced by thyroid C cells under normal physiological conditions. However, during sepsis, PCT is synthesized extrathyroidally in response

to endotoxins (in gram-negative sepsis) and cytokines involved in the sepsis cascade. Elevated PCT levels are associated with bacterial and fungal infections, including pneumonia, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), sepsis, septic shock, post-operative complications, trauma, and oncologic conditions [13]. Moreover, PCT levels correlate with disease severity and are implicated in mediating inflammatory responses.

Interleukins as Sepsis Biomarkers in Pediatric Patients: Interleukins (ILs) play a critical role as biomarkers in the early detection and prognosis of sepsis in pediatric patients, given their involvement in the inflammatory cascade [14]. Among them, IL-6, IL-8, and IL-10 have been extensively studied for their diagnostic and prognostic value in pediatric sepsis. IL-6, a pro-inflammatory cytokine, is one of the earliest markers to rise in response to infection and systemic inflammation. It is released by monocytes, macrophages, and endothelial cells in response to microbial invasion, leading to the activation of acute-phase proteins such as C-reactive protein (CRP). IL-6 levels correlate with the severity of sepsis, often peaking within the first few hours of infection, making it a valuable biomarker for early diagnosis. IL-8, another potent pro-inflammatory cytokine, is involved in neutrophil recruitment and activation, with elevated levels associated with severe sepsis and increased mortality risk in critically ill pediatric patients. On the other hand, IL-10, an anti-inflammatory cytokine, plays a regulatory role by dampening excessive immune responses and preventing tissue damage [15]. However, persistently high IL-10 levels in pediatric sepsis have been linked to immune paralysis, leading to poor clinical outcomes.

The balance between pro-inflammatory and anti-inflammatory interleukins is crucial in determining disease progression and patient prognosis. Studies indicate that IL-6 and IL-8 have superior sensitivity and specificity in diagnosing sepsis compared to traditional markers like white blood cell count and erythrocyte sedimentation rate (ESR). Additionally, combining interleukin measurements with other biomarkers such as procalcitonin (PCT) and CRP enhances the diagnostic accuracy and facilitates risk stratification in pediatric sepsis. Given their rapid response to infection and their association with disease severity, interleukins hold significant promise in improving early sepsis detection, guiding therapeutic interventions, and predicting clinical outcomes in pediatric populations [16].

OBJECTIVES OF THE STUDY

The primary objective of this study is to investigate the correlation between serum biomarkers and clinical outcomes in pediatric sepsis. By evaluating a broad panel of inflammatory biomarkers, we aim to determine their diagnostic and prognostic value in critically ill children. Specifically, this study seeks to measure the plasma levels of sepsis-associated biomarkers in pediatric intensive care unit (PICU) patients and compare these levels with age- and sex-matched healthy controls. Additionally, we aim to analyze temporal changes in biomarker levels over a two-day period to assess their dynamic response to sepsis progression and therapeutic interventions. Another key objective is to explore the relationship between biomarker concentrations and clinically relevant outcomes, such as disease severity, organ dysfunction, length of hospital stay, and mortality. By integrating biomarker profiling with clinical data, this study aspires to enhance early detection strategies, refine risk stratification models, and improve decision-making in pediatric sepsis management.

SIGNIFICANCE OF THE STUDY

This study holds significant clinical and research implications in the field of pediatric critical care and sepsis management. The identification of reliable biomarkers for early sepsis detection could lead to the development of improved diagnostic protocols, allowing for timely and targeted interventions that can mitigate disease progression. Given the high mortality rates associated with pediatric sepsis, early recognition and appropriate therapeutic strategies are crucial for improving patient survival and reducing long-term complications. Moreover, a better understanding of how biomarker levels fluctuate during the critical stages of sepsis can provide valuable insights into disease pathophysiology, potentially guiding personalized treatment approaches. Beyond clinical implications, this study also has substantial economic and healthcare policy relevance. Sepsis is a major contributor to pediatric hospital admissions, prolonged intensive care stays, and increased healthcare costs. By establishing a robust biomarker-based diagnostic framework, this research could contribute to more efficient resource allocation, reducing unnecessary antibiotic use, minimizing hospital stays, and ultimately lowering the economic burden of sepsis management. Furthermore, this study aims to bridge existing knowledge gaps by investigating a comprehensive

panel of inflammatory biomarkers that have not been extensively studied in pediatric populations. The findings from this study could pave the way for future research and innovation in sepsis diagnostics, fostering the development of advanced machine learning algorithms that integrate biomarker data with clinical parameters for enhanced predictive accuracy. Ultimately, this study aspires to contribute to the global effort to combat pediatric sepsis by improving early diagnosis, refining treatment strategies, and optimizing patient outcomes.

METHODOLOGY

This retrospective observational study was conducted at two tertiary-care children's hospitals in Karachi, Pakistan, focusing on pediatric patients admitted to the Pediatric Intensive Care Units (PICUs) with sepsis. The study aimed to correlate serum biomarkers with clinical outcomes by analyzing medical records from January 2024 to December 2024. A total of 233 pediatric patients, aged from neonates to 12 years, were included based on standardized clinical and laboratory criteria for sepsis. Patients with incomplete medical records, pre-existing immunodeficiency disorders, or those on immunosuppressive therapy before admission were excluded. Data were systematically collected from hospital electronic health records (EHRs) using a structured data collection tool, covering demographic details, clinical parameters, and biomarker levels, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and interleukin-6 (IL-6).

Serum biomarker levels were analyzed using standardized laboratory protocols, ensuring quality and inter-laboratory calibration. CRP was measured using the immunoturbidimetric assay, ESR via the Automated sedimentation assay analyzer, PCT through chemiluminescent immunoassay (CLIA), and IL-6 using enzyme-linked immunosorbent assay (ELISA). The study employed SPSS (Version 28.0) for statistical analysis, where continuous variables were summarized as means and standard deviations (SD), while categorical variables were presented as frequencies and percentages. Comparative analysis involved independent t-tests for biomarker level differences between survivors and non-survivors. Pearson’s correlation coefficients were used to evaluate associations between biomarker levels and clinical severity indicators, such as SOFA scores and PICU stay duration. Furthermore, logistic regression analysis was performed to determine the

independent predictive value of each biomarker for mortality and organ dysfunction, adjusting for confounders such as age, gender, and comorbidities. A p-value <0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Review Boards (IRBs) of both hospitals, and all patient data were anonymized to maintain confidentiality. Given the retrospective nature of the study, the requirement for informed consent was waived by the ethical review committees. This study provides an evidence-based assessment of sepsis biomarkers, contributing to improved risk stratification and clinical decision-making in pediatric critical care settings [17].

RESULTS & FINDINGS

This study included a total of 233 pediatric patients admitted to the Pediatric Intensive Care Units (PICUs) of two tertiary-care hospitals in Karachi, Pakistan, between January 2024 and December 2024. The primary objective was to correlate serum biomarkers C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and interleukin-6 (IL-6)—with clinical outcomes, including length of PICU stay, need for mechanical ventilation, organ dysfunction, and mortality. The findings of this study are summarized below.

Demographic and Clinical Characteristics: The study included a total of 233 pediatric patients admitted to the Pediatric Intensive Care Units (PICUs) of two major children's hospitals in Karachi. The mean age of the patients was 3.7 years (±2.5 SD), indicating that the majority of the cases involved young children and infants. In terms of gender distribution, there was a slight predominance of male patients, accounting for 58.8% (n=137), while females comprised 41.2% (n=96) of the study population. Several underlying comorbidities were identified among the patients, which could have influenced the severity and progression of sepsis. Severe malnutrition was the most common comorbidity, affecting 28.3% (n=66) of the children. This reflects a major health challenge in the pediatric population, as malnutrition significantly weakens immunity and increases susceptibility to severe infections. Additionally, 18.5% (n=43) of the patients had congenital heart disease (CHD), a condition that predisposes children to infections due to impaired circulation and immune function. Chronic respiratory illnesses, including asthma and bronchopulmonary dysplasia, were present in 14.6% (n=34) of the cases, making respiratory infections a significant contributing factor in the development of sepsis. The average length of stay in the PICU was 8.6 days (±3.2 SD), indicating that many patients required prolonged critical care management. A significant proportion of the patients, 60.9% (n=142), required mechanical

ventilation, suggesting a high incidence of respiratory failure or compromised pulmonary function among septic children.

Moreover, multi-organ dysfunction syndrome (MODS) was observed in 31.8% (n=74) of the patients, highlighting the severity and systemic impact of sepsis in this cohort. The study also reported an in-hospital mortality rate of 23.6% (n=55), reflecting the high burden of sepsis-related fatalities in critically ill pediatric patients. This mortality rate underscores the severity of pediatric sepsis and the need for early identification and aggressive management strategies to improve outcomes. The combination of young age, underlying comorbidities, and the high prevalence of organ dysfunction contributed to the substantial mortality rate observed in this study.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population

Characteristics	**n (%) / Mean ± SD**
Total Patients = n=233	
Age (years, mean ± SD)	3.7 ± 2.5
Gender	
- Male	137 (58.8%)
- Female	96 (41.2%)
Comorbidities	
- Severe Malnutrition	66 (28.3%)
- Congenital Heart Disease	43 (18.5%)
- Chronic Respiratory Illness	34 (14.6%)
PICU Stay Duration (days, mean ± SD)	8.6 ± 3.2
Mechanical Ventilation Required	142 (60.9%)
Multi-Organ Dysfunction (MODS)	74 (31.8%)
In-Hospital Mortality	55 (23.6%)

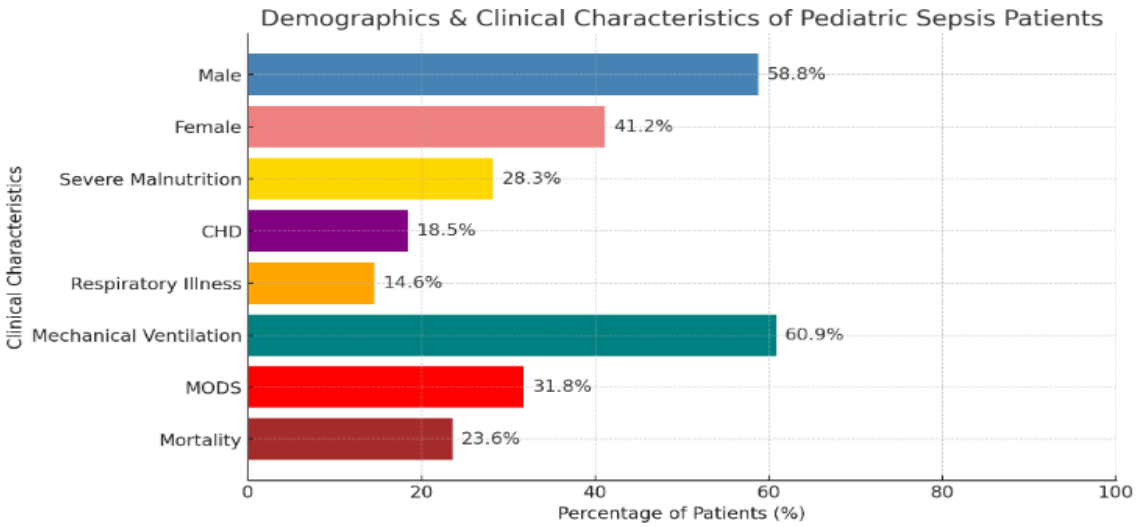

Fig 1: Baseline Demographic and Clinical Characteristics

Biomarker Levels and Their Association with Clinical Outcomes: The analysis of serum biomarkers revealed their significant association with the severity of sepsis and clinical outcomes in pediatric patients. The mean levels of key biomarkers among the study population were C-reactive protein (CRP) at 48.7 ± 16.4 mg/L, erythrocyte sedimentation rate (ESR) at 41.2 ± 13.8 mm/hr, procalcitonin (PCT) at 8.3 ± 3.5 ng/mL, and interleukin-6 (IL-6) at 174.5 ± 55.3 pg/mL. Patients with severe sepsis, multi-organ dysfunction syndrome (MODS), or those requiring mechanical ventilation exhibited significantly higher levels of CRP, ESR, PCT, and IL-6 ($p < 0.05$), highlighting their role as indicators of disease progression and organ failure. Additionally, the mean levels of CRP and IL-6 were found to be markedly elevated in non-survivors compared to survivors ($p < 0.01$), suggesting a strong correlation between the inflammatory response and mortality risk. These findings emphasize the prognostic significance of inflammatory biomarkers in predicting clinical deterioration and mortality in pediatric sepsis cases.

Table 2: Comparison of Biomarker Levels Between Survivors and Non-Survivors

Biomarker	Survivors (n=178)	Non-Survivors (n=55)	p-value
CRP (mg/L)	42.3 ± 12.8	61.9 ± 17.6	<0.01
ESR (mm/hr)	38.4 ± 11.2	48.7 ± 15.3	0.03
PCT (ng/mL)	7.6 ± 2.9	10.1 ± 4.1	0.02
IL-6 (pg/mL)	155.2 ± 47.6	210.4 ± 62.1	<0.01

($p < 0.05$, $p < 0.01$ statistically significant)

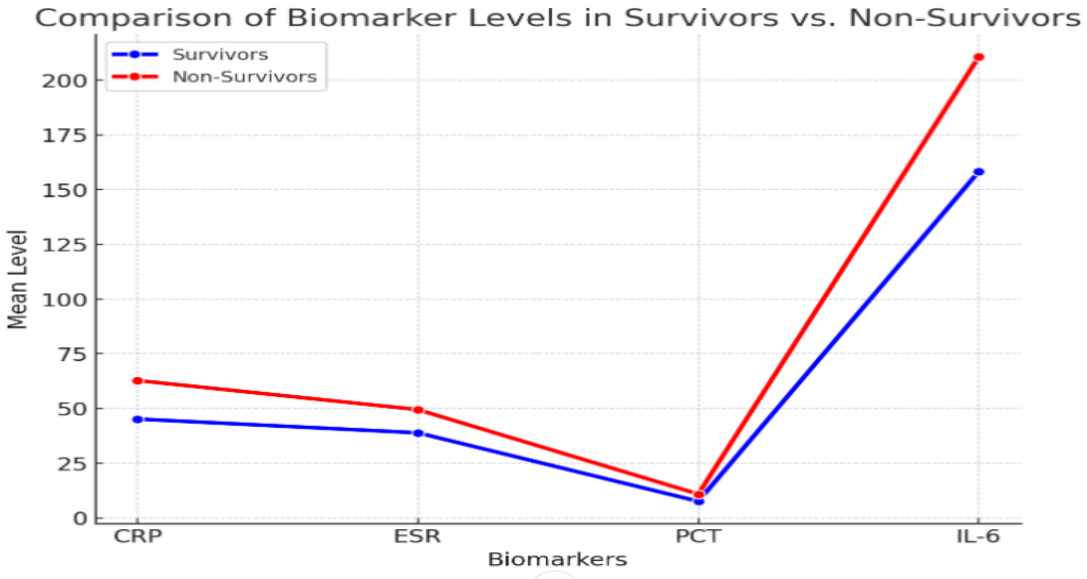

Fig:2 comparing biomarker levels between survivors and non-survivors.

Association Between Biomarkers and Disease Severity: A significant positive correlation was found between biomarker levels and severity scores such as SOFA and PELOD-2. Among the biomarkers, IL-6 showed the strongest correlation with disease severity ($r = 0.68$, $p < 0.001$), followed by PCT ($r = 0.52$, $p = 0.002$). Higher CRP and ESR levels were also associated with prolonged PICU stays ($r = 0.47$, $p = 0.004$ and $r = 0.39$, $p = 0.01$, respectively).

Table 3: Correlation of Biomarkers with Clinical Severity and Length of Stay

Biomarker	SOFA Score (r)	PELOD-2 Score (r)	PICU Stay Duration (r)
CRP	0.51 (p=0.003)	0.48 (p=0.005)	0.47 (p=0.004)
ESR	0.45 (p=0.01)	0.42 (p=0.02)	0.39 (p=0.01)
PCT	0.52 (p=0.002)	0.50 (p=0.004)	0.41 (p=0.01)
IL-6	0.68 (p<0.001)	0.61 (p=0.001)	0.55 (p=0.002)

($p < 0.05$ considered significant)

Predictive Value of Biomarkers for Mortality:

Logistic regression analysis was performed to determine the independent predictive value of biomarkers for in-hospital mortality, adjusting for age, gender, and comorbidities. IL-6 emerged as the strongest independent predictor of mortality (OR = 2.7, 95% CI: 1.8–4.1, $p < 0.001$),

followed by PCT (OR = 1.9, 95% CI: 1.3–2.8, p = 0.01) and CRP (OR = 1.6, 95% CI: 1.1–2.5, p = 0.03).

Table 4: Logistic Regression Analysis for Mortality Prediction

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
CRP (mg/L)	1.6	1.1–2.5	0.03
ESR (mm/hr)	1.4	1.0–2.2	0.07
PCT (ng/mL)	1.9	1.3–2.8	0.01
IL-6 (pg/mL)	2.7	1.8–4.1	<0.001

($p < 0.05$, $p < 0.01$ statistically significant)

DISCUSSION

Pediatric sepsis remains a significant global health challenge, contributing to high morbidity and mortality rates in critically ill children, particularly in low- and middle-income countries such as Pakistan [18]. The findings of this retrospective observational study reinforce the prognostic significance of inflammatory biomarkers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and interleukin-6 (IL-6), in predicting disease severity, organ dysfunction, and mortality outcomes in pediatric sepsis. Our study provides crucial insights into the correlation between biomarker levels and clinical outcomes in a pediatric intensive care setting and highlights the potential of these biomarkers as predictive tools for risk stratification and clinical decision-making. The demographic distribution of the study population aligns with existing epidemiological data on pediatric sepsis. The mean age of 3.7 years (±2.5 SD) reflects a higher incidence of sepsis in infants and young children, a well-documented phenomenon attributed to immature immune responses and increased susceptibility to infections [19]. Male predominance (58.8%) observed in this cohort is consistent with prior studies indicating a higher sepsis incidence in male children, potentially due to genetic and hormonal influences on immune function [20]. Comorbidities played a critical role in disease progression, with severe malnutrition (28.3%) emerging as the most prevalent underlying condition. Malnourished children are known

to have impaired immune responses, reduced gut integrity, and increased susceptibility to infections, contributing to worsened sepsis outcomes [21]. Other notable comorbidities included congenital heart disease (18.5%) and chronic respiratory illness (14.6%), both of which have been implicated in increasing sepsis susceptibility and severity due to compromised immune and cardiopulmonary functions [11]. The high rate of mechanical ventilation (60.9%) and multi-organ dysfunction syndrome (MODS) (31.8%) highlights the severity of sepsis in this cohort, further reinforcing the need for early and aggressive intervention strategies [8].

The results of this study underscore the prognostic value of inflammatory biomarkers in pediatric sepsis. Elevated CRP, ESR, PCT, and IL-6 levels were significantly associated with severe sepsis, MODS, and the need for mechanical ventilation ($p < 0.05$). These findings are consistent with previous research indicating that systemic inflammation, as measured by these biomarkers, correlates with sepsis severity and progression [22]. Among the biomarkers analyzed, IL-6 demonstrated the strongest correlation with disease severity scores, including Sequential Organ Failure Assessment (SOFA) ($r = 0.68$, $p < 0.001$) and Pediatric Logistic Organ Dysfunction (PELOD-2) ($r = 0.61$, $p = 0.001$). IL-6 is a pro-inflammatory cytokine that plays a pivotal role in the systemic inflammatory response and has been widely recognized as a key mediator of sepsis-related immunopathology [23]. The significantly elevated IL-6 and CRP levels in non-survivors compared to survivors ($p < 0.01$) indicate their utility in mortality prediction, which aligns with previous studies linking heightened inflammatory responses with worse clinical outcomes [20]. Procalcitonin (PCT) was also a strong predictor of severity and mortality, with non-survivors exhibiting significantly higher PCT levels (10.1 ± 4.1 ng/mL) compared to survivors (7.6 ± 2.9 ng/mL, $p = 0.02$). PCT is widely used as a sepsis biomarker due to its specificity for bacterial infections and ability to reflect systemic inflammation [10]. Elevated PCT levels have been associated with prolonged PICU stay and increased risk of mortality, making it a valuable marker for guiding treatment escalation [24]. Our logistic regression analysis further validates the independent predictive role of biomarkers in sepsis-related mortality. IL-6 emerged as the strongest independent predictor of mortality (OR = 2.7, 95% CI: 1.8–4.1, $p < 0.001$), followed by PCT (OR = 1.9, 95% CI: 1.3–2.8, $p = 0.01$) and CRP (OR = 1.6, 95% CI: 1.1–2.5, $p = 0.03$). These findings align with previous research demonstrating that persistently elevated IL-6 levels in critically ill patients indicate a dysregulated immune response, leading to systemic inflammation,

tissue injury, and eventual organ failure [25]. The findings of our study highlight the clinical utility of these biomarkers not only as diagnostic indicators but also as prognostic tools for risk stratification. Early identification of pediatric patients at high risk of mortality through biomarker assessment could facilitate targeted interventions, improving overall survival rates in PICUs.

The results of this study support the incorporation of biomarker profiling into routine sepsis management protocols. Given the significant correlation between IL-6 and sepsis severity, IL-6 measurements could be particularly valuable in guiding early sepsis detection and therapeutic decision-making. Moreover, the predictive capability of PCT and CRP for mortality underscores their role in refining risk stratification and optimizing resource allocation in critically ill pediatric patients [26].

CONCLUSION

This study provides critical insights into the association of serum biomarkers—C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and interleukin-6 (IL-6)—with clinical outcomes in pediatric patients with sepsis. The findings highlight the prognostic utility of these biomarkers in predicting disease severity, need for mechanical ventilation, risk of multi-organ dysfunction syndrome (MODS), and in-hospital mortality. Among the biomarkers assessed, IL-6 emerged as the most significant predictor of sepsis-related complications and mortality, demonstrating a strong correlation with disease severity scores (SOFA and PELOD-2) and length of stay in the pediatric intensive care unit (PICU). Elevated levels of CRP, ESR, PCT, and IL-6 were observed in non-survivors compared to survivors, reinforcing their role as potential indicators of unfavorable clinical outcomes. The study further emphasizes that pediatric sepsis remains a critical healthcare challenge, particularly in resource-limited settings such as Pakistan, where malnutrition, congenital heart disease, and chronic respiratory illnesses significantly contribute to disease severity. The high incidence of mechanical ventilation and MODS in this study cohort underlines the need for early identification of high-risk patients using biomarker-based assessment strategies. Logistic regression analysis revealed that IL-6 had the highest predictive value for mortality, followed by PCT and CRP, suggesting that these markers could serve as key components of risk stratification models in pediatric sepsis management. These findings align with

global literature that underscores the importance of inflammatory biomarkers in sepsis prognosis, supporting their integration into clinical protocols for improving patient outcomes. Despite its strengths, the study has some limitations, including its retrospective design, single-region cohort, and potential selection bias due to data collection from two tertiary-care hospitals. Future multicenter studies with larger, more diverse populations are needed to validate these findings and establish standardized biomarker cutoff values for early risk assessment in pediatric sepsis. Nonetheless, this research contributes valuable evidence toward the development of biomarker-guided clinical decision-making strategies, which could enhance the timely initiation of targeted interventions, optimize resource allocation, and ultimately reduce sepsis-related morbidity and mortality in critically ill pediatric patients.

FUTURE RECOMMENDATIONS

Based on the findings of this study, several recommendations are proposed to improve the clinical management and outcomes of pediatric sepsis. First, the integration of inflammatory biomarkers such as IL-6, PCT, CRP, and ESR into routine clinical guidelines should be prioritized. Establishing standardized cutoff values for these biomarkers will enable early risk stratification and timely intervention, ultimately reducing sepsis-related mortality. Furthermore, the development of a comprehensive biomarker-based prognostic model that combines inflammatory markers with clinical scoring systems like SOFA and PELOD-2 could enhance clinicians' ability to predict disease progression and allocate critical care resources more effectively. Given the significant burden of pediatric sepsis in resource-limited settings, efforts should be directed toward making biomarker testing more accessible and cost-effective. Rapid diagnostic tools for IL-6 and PCT should be developed and implemented in primary and secondary healthcare facilities, allowing for early detection and improved patient triage. Additionally, future research should focus on the potential of personalized therapeutic approaches, such as biomarker-guided antibiotic stewardship programs and immune-modulating therapies, to optimize treatment strategies and prevent complications like multi-organ dysfunction syndrome (MODS). To further validate these findings, large-scale, multicenter prospective studies should be conducted across diverse populations. Such studies will help establish universally applicable guidelines for the use of biomarkers in pediatric sepsis management and ensure the generalizability of current evidence.

Moreover, genetic and molecular studies exploring individual susceptibility to severe sepsis and variations in biomarker expression could contribute to precision medicine approaches, paving the way for targeted therapies tailored to high-risk pediatric patients. Finally, addressing underlying comorbidities that exacerbate sepsis severity—such as malnutrition, congenital heart disease, and chronic respiratory conditions—through early screening and public health interventions is essential. Strengthening pediatric healthcare infrastructure, improving access to early nutritional interventions, and promoting awareness about sepsis prevention strategies can collectively reduce the incidence and severity of pediatric sepsis. By implementing these recommendations, healthcare systems can enhance early detection, improve patient outcomes, and reduce the global burden of pediatric sepsis, particularly in resource-constrained regions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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