

Proteomic biomarkers for early diagnosis and prognosis in pediatric sepsis

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Abstract

BACKGROUND

Early diagnosis of pediatric sepsis is difficult because of the lack of specific clinical signs and limitations of standard biomarkers. Proteomics is a promising approach because it can identify disease-specific protein signatures.

AIM

To systematically evaluate the current literature on the application of proteomics in pediatric sepsis, review and evaluate the current evidence on proteomic biomarkers for diagnosing and predicting pediatric sepsis.

METHODS

This is a systematic review with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses-informed, structured search and transparent study-selection reporting. A structured literature search was conducted in PubMed, Scopus, and Web of Science up to January 2025. Studies involving pediatric patients (ages 0-18) with sepsis that used proteomic platforms and reported diagnostic or prognostic outcomes were included.

RESULTS

Four studies met the inclusion criteria. Identified biomarkers included in-

terleukin-27, signal transducer and activator of transcription 3, haptoglobin, serum amyloid A 1/2, soluble CD25, and leucine-rich alpha-2-glycoprotein 1. Sensitivities ranged from 60% to 86%, and specificities ranged from 75% to 92%. Multi-marker panels demonstrated superior diagnostic performance compared to single markers. Biomarkers were detectable within 2-6 hours of symptom onset. The analytical methods used varied and included enzyme-linked immunosorbent assays, liquid chromatography-tandem mass spectrometry, and SOMAscan. Most studies were exploratory and lacked external validation; they also used small, heterogeneous cohorts.

CONCLUSION

Proteomics shows promise for earlier and more precise diagnostics of pediatric sepsis, but clinical translation is limited by small, single-center cohorts; age-dependent variability without developmental reference ranges; scarce longitudinal profiling; and minimal external validation. The priority now is multicenter, age-stratified, longitudinal studies with real-world comparators.

Key Words: Sepsis; Pediatric sepsis; Biomarkers; Proteomics; Multi-omics; Pediatric intensive care unit; Pediatrics

Core Tip: Pediatric sepsis requires rapid and reliable “rule-in” tools upon presentation. This systematic review summarizes four pediatric proteomics studies and presents a practical pathway. Single markers, such as interleukin-27, serum amyloid A 1, soluble CD25, and leucine-rich alpha-2-glycoprotein 1, demonstrate high specificity for early diagnosis. The infant-focused combination of haptoglobin and thrombospondin 1 improves short-term risk stratification. We explain why age matters: Noting that immune maturation shifts effect sizes and may necessitate age-adjusted cut-points and neonatal-specific panels. We also map discovery platforms (aptamer/mass spectrometry) to rapid 3-5-plex immunoassays that are suitable for emergency department and pediatric intensive care unit use. Rather than offering pooled estimates, the systematic review provides translational guidance aimed at accelerating the deployment of clinically useful pediatric sepsis testing.

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INTRODUCTION

Sepsis is a life-threatening syndrome that arises from an excessive host response to infection. This response can result in organ dysfunction and high mortality[1,2]. Among pediatric populations, sepsis is a significant global health concern, causing an estimated 2.9 million deaths each year[3]. Despite improvements in pediatric intensive care and antimicrobial therapy availability, early sepsis diagnosis in children is challenging[4]. This is largely due to its non-specific clinical presentation in the early stages, which can include symptoms such as fever, lethargy, poor feeding, or irritability. These signs commonly overlap with those of other childhood infections or inflammatory conditions[5].

The difficulty of identifying pediatric sepsis in a timely manner is further complicated by fundamental differences in the immune systems of children and adults, as well as differences among children of different ages. Neonates and infants have immature adaptive immune responses and predominantly rely on innate mechanisms to clear pathogens, which increases their vulnerability to invasive infections[6,7]. Older children are more immunocompetent but still experience age-dependent variations in inflammatory and immunoregulatory responses that can influence the course of sepsis and complicate diagnosis[8,9].

Traditional biomarkers, such as C-reactive protein (CRP) and procalcitonin (PCT), are commonly used in clinical settings to aid in the diagnosis of sepsis. However, these markers have significant limitations. For example, CRP, an acute-phase reactant, is elevated in various inflammatory conditions, including both infectious and non-infectious ones, which reduces its diagnostic specificity[10,11]. Although PCT is more specific for bacterial infections, its levels can also increase in cases of trauma, surgery, or systemic inflammation unrelated to sepsis, which can lead to false-positive results [12,13]. Furthermore, both CRP and PCT reflect downstream inflammatory activity rather than early immunopathological events, which limits their utility in the early detection of sepsis or the prediction of outcomes[14,15].

The heterogeneity of pediatric immune responses and the limited performance of traditional biomarkers highlight the necessity of more precise, biologically informed diagnostic strategies[16]. In recent years, high-throughput technologies, collectively referred to as “omics” approaches, have gained traction in biomedical research. Proteomics, in particular, offers a promising avenue for sepsis research due to its ability to assess dynamic changes in protein expression, post-translational modifications, and signaling cascades relevant to host-pathogen interactions and immune dysregulation[17, 18]. Proteomic techniques, such as mass spectrometry (MS) and aptamer-based platforms, can identify protein signatures that may serve as diagnostic and prognostic biomarkers with greater sensitivity and specificity than traditional methods.

Proteomics is especially valuable in the study of pediatric sepsis due to the age-specific nature of immune responses. Several candidate protein biomarkers have been identified in emerging studies, including interleukin-27 (IL-27), haptoglobin (HP), serum amyloid A 1 (SAA1), signal transducer and activator of transcription 3 (STAT3), and soluble

CD25 (sCD25)[19]. These biomarkers show potential for early detection and risk stratification in septic children[20-23]. These discoveries highlight the potential of proteomic analysis to improve clinical decision-making. However, despite growing interest and encouraging findings, many of these biomarkers remain in the discovery phase with limited validation in large, diverse pediatric patient groups. Challenges such as variability in biomarker expression by age, disease severity, and comorbid conditions, as well as technical barriers to routine implementation, continue to hinder clinical translation.

This systematic review aims to systematically evaluate the current literature on the application of proteomics in pediatric sepsis, assess the diagnostic and prognostic performance of the identified biomarkers, and outline the associated opportunities and limitations of integrating proteomic tools into pediatric critical care. By synthesizing the available evidence, this systematic review seeks to inform future research and contribute to the development of more accurate, age-sensitive, and rapid diagnostic strategies for pediatric sepsis.

MATERIALS AND METHODS

A structured literature review was conducted to identify relevant studies focusing on proteomic biomarkers for diagnosing or predicting the prognosis of pediatric sepsis. Searches were performed across three major biomedical databases: (1) PubMed; (2) Scopus; and (3) Web of Science. The search covered the period from database inception through January 2025. The search strategy used a combination of Medical Subject Headings and free-text terms such as “pediatric sepsis”, “proteomics”, “biomarkers”, “protein signature”, “early diagnosis of sepsis”, and “proteomics in pediatric patients”. Boolean operators and wildcards were used to refine and expand the scope of results where appropriate. The number of results retrieved for each search term is summarized in Table 1. Additionally, the reference lists of key articles were manually reviewed to identify relevant studies not captured by the database searches. Studies were included if they focused on pediatric patients (defined as individuals aged 0-18 years, but excluding the newborns) and utilized proteomic methodologies to identify or evaluate sepsis-related biomarkers.

Eligible studies were required to report diagnostic or prognostic outcomes such as sensitivity, specificity, or the clinical performance of proteomic markers. Accepted proteomic techniques included MS-based platforms [e.g., liquid chromatography-tandem MS (LC-MS/MS)], two-dimensional gel electrophoresis, and aptamer-based assays (e.g., SOMAscan). Validated follow-up methods, such as enzyme-linked immunosorbent assays (ELISA), were also accepted. Although we intended to evaluate children from birth to 18 years of age, we found that many eligible studies excluded neonates and young infants or lacked neonatal subgroup analyses. Therefore, we report the age ranges represented by each included study, highlight gaps in neonatal evidence, and treat age as a source of effect-modifying heterogeneity that limits the generalizability of results across developmental stages.

Studies employing multi-omics approaches were included if the proteomic component was clearly described and contributed substantially to the findings. Studies lacking a pediatric focus or failing to report sepsis as a primary outcome were excluded from the analysis. Also, research that did not utilize proteomic tools or failed to provide adequate methodological details regarding biomarker discovery was excluded. Articles published before 2000 were excluded because earlier proteomic technologies were outdated. Additionally, conference abstracts, editorials, and narrative reviews without original data were excluded from the final synthesis.

The initial search yielded 212 studies. After removing 53 duplicates, we screened 159 titles and abstracts. Based on the predefined inclusion and exclusion criteria, 124 studies were excluded. The full texts of the remaining 35 potentially relevant articles were re-viewed. Of these, 30 studies were excluded due to insufficient methodological detail, incomplete reporting of biomarker data, or lack of pediatric relevance. Four studies met all the eligibility criteria and were included in the final review. The study selection process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as illustrated in Figure 1.

Any PRISMA-style elements (e.g., search description, counts of screened records, flow diagram) serve as descriptive aids and do not imply full PRISMA compliance. Our search was purposive rather than exhaustive, so relevant studies beyond those discussed may exist. Our objective was to contextualize concepts, platforms, and translational implications in pediatric sepsis proteomics rather than generate pooled effect estimates.

Statistical analysis

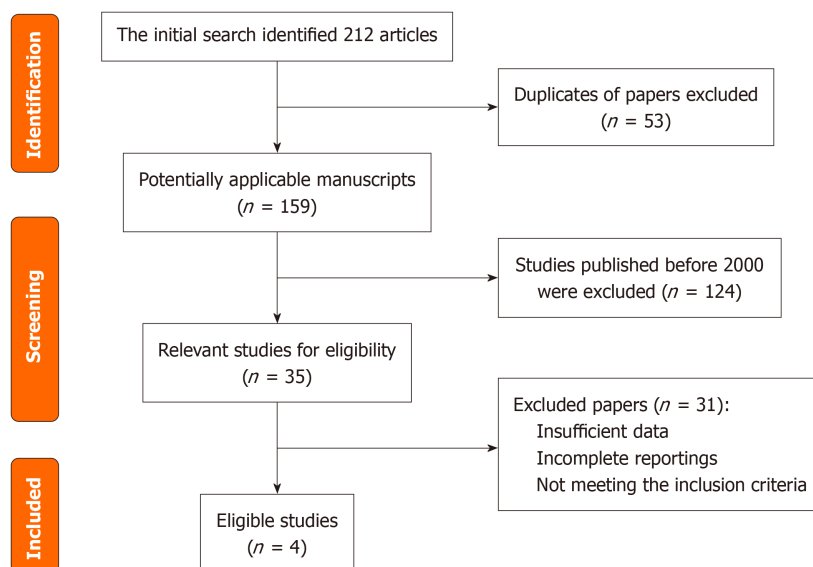
Data were extracted from the selected studies using a standardized form to ensure consistency and accuracy. Extracted variables included study design; year and location of publication; number and age range of patients and controls; proteomic platform used; biomarkers identified; and diagnostic or prognostic performance metrics, such as sensitivity, specificity, and area under the receiver operating characteristic curve. Where applicable, additional data regarding sample types, timing of biomarker assessment, and clinical context were collected as well.

RESULTS

This systematic review included a total of four original studies, each of which investigated the utility of proteomic biomarkers for the early diagnosis or prognostication of pediatric sepsis. The studies varied in design, analytical platforms, and pediatric populations. However, all of the studies employed validated proteomic methods and provided measurable diagnostic performance indicators. The four studies also varied in sample size and patient characteristics. The

Table 1 Results of database search

Key terms for search	Results from PubMed	Results from Scopus	Results from Web of Science
Pediatric sepsis	25796	13583	13458
Proteomics in sepsis	996	826	522
Sepsis biomarkers	14390	11214	6977
Haptoglobin	11690	18786	10114
Interleukin-27	2219	2179	2452

**Figure 1 Flowchart of study selection.**

number of sepsis cases ranged from 10 to 231, and the number of individuals in the control groups ranged from 5 to 61. Participants spanned a wide pediatric age range, from neonates to 16-year-olds, reflecting age-specific differences in immune and inflammatory responses. Sample collection was consistently performed during the early phase of illness to ensure that the proteomic changes captured reflected the early dynamics of sepsis. Table 2 concentrates cohort design, timing, comparators, and platform pipelines for reproducibility[20-23].

Several promising biomarkers were identified across the selected studies. For example, Wong *et al*[20] reported that IL-27 demonstrated high specificity (92%) but moderate sensitivity (60%) in distinguishing bacterial sepsis from sterile inflammation in children. This suggests that IL-27 may serve as a valuable rule-in marker. Shubin *et al*[23] found elevated STAT3 and IL-1 α levels in the plasma of septic patients, with STAT3 showing 86% sensitivity and 82% specificity. These findings suggest its potential as a rapid and reliable diagnostic indicator. Luo *et al*[21] identified HP, thrombospondin 1 (THBS1), and SAA1/2 as differentially expressed proteins in septic infants. Validation indicated moderate diagnostic accuracy, with sensitivity and specificity of 73% and 77%, respectively. Finally, Pilar-Orive *et al*[22] proposed a diagnostic panel consisting of sCD25, SAA1, and leucine-rich alpha-2-glycoprotein 1 (LRG1). This panel achieved balanced performance, suggesting the advantage of multiplexed biomarker panels over individual markers. While no specific performance metrics were provided, the extent of differential expression highlights the complexity of proteomic alterations in pediatric sepsis.

The time to biomarker elevation ranged from two to six hours after the onset of sepsis, which is clinically significant for making early therapeutic decisions. For example, HP (Luo *et al*[21]) and STAT3 (Shubin *et al*[23]) increased within 2-4 hours, while IL-27 and the three-marker panel proposed by Pilar-Orive *et al*[22] showed increases within 4-6 hours. These findings support the integration of these biomarkers into early diagnostic workflows, particularly in high-acuity settings.

All of the included studies used serum or plasma samples for analysis, and the analytical methods varied by platform. These methods included ELISA, chemiluminescent enzyme immunoassays (CLEIA), immunoturbidimetric assays, fluorescence immunoassays, SOMAscan aptamer-based arrays, and LC-MS/MS. While ELISA and CLEIA are easily translatable to clinical practice, more advanced methods, such as SOMAscan and LC-MS/MS, offer greater resolution and sensitivity, yet they remain largely in the research phase due to cost and technical complexity. Table 3 summarizes the area under the receiver operating characteristic curve, sensitivity, specificity, and thresholds by biomarker/panel and clinical purpose in each study.

The studies provided qualitative insights that reinforced several consistent biological themes, including dysregulation of inflammatory pathways, activation of the complement and coagulation cascades, and disruption of cellular signaling.

Table 2 Comparative characteristics of the four included studies

Ref.	Wong <i>et al</i> [20]	Luo <i>et al</i> [21]	Pilar-Orive <i>et al</i> [22]	Shubin <i>et al</i> [23]
Setting/design	17-center PICU; prospective observational diagnostic biomarker study	Single-center; nested case-control; pneumonia-derived sepsis	Single-center; analytical observational case-control study	Single-center PICU/cardiac intensive care unit; prospective observational, proteomics
Number (analyzed) and age	231 (<i>vs</i> 61 control group); noted multicenter; ≤ 10 years	90 discovery samples pooled (20 controls); enzyme-linked immunosorbent assays validation ($n = 35$). Age strata: Infants (7-12 months), toddlers (13-36 months)	40 septic children (<i>vs</i> 24 healthy donors); 1 month to 16 years	35 sepsis (<i>vs</i> 28 control); 1 sepsis outlier removed 34 sepsis analyzed, 1-8 years
Specimen and timing	Serum; within first 24 hours	Plasma; processed ≤ 24 hours; -80°C storage; top-12 depletion	Serum; single draw (study baseline)	Serum; day-1 post-presentation/CPB (per cohort definitions)
Comparators	Systemic inflammatory response syndrome (culture-neg) <i>vs</i> sepsis/septic shock (culture-pos)	Within-age outcome groups (improved <i>vs</i> no-improve <i>vs</i> non-survivors)	Healthy donors	Post-CPB infection-negative systemic inflammation (non-infectious systemic inflammation)
Sepsis marker	Interleukin-27	Haptoglobin, thrombospondin 1, SAA1/2	Soluble CD25, SAA1, leucine-rich alpha-2-glycoprotein 1	Signal transducer and activator of transcription 3
Response time	Rises within 4-6 hours	Rises within 2-4 hours	Rises within 4-6 hours	Rises within 2-4 hours
Clinical significance	Early diagnosis of sepsis; monitoring post-surgery recovery	Early diagnosis of sepsis; optimizing antibiotic treatment	Diagnosis of specific pathogens; prognosis of sepsis severity	Early diagnosis of sepsis; prognosis for severe sepsis
Strengths	High specificity for bacterial infection; rapid response	Good specificity for bacterial infections; rapid biomarker rise	Targeted multi-marker approach; provides pathogen-specific diagnostic cues	High specificity for sepsis; useful for early prognosis
Limitations	Low sensitivity in localized infections (false negatives)	False positives in non-bacterial inflammation; expensive test	Limited generalizability; potential for false positives in specific cases	Expensive; limited accessibility

CPB: Cardiopulmonary bypass; PICU: Pediatric intensive care unit; SAA: Serum amyloid A.

Luo *et al*[21] noted age-specific variation in biomarker expression, emphasizing the need for age-adjusted reference ranges and diagnostic cutoffs. Several authors also highlighted the potential of biomarker panels to improve diagnostic precision, reduce false positives, and more accurately stratify disease severity compared to single-marker approaches.

Taken together, these findings provide preliminary, yet promising, evidence for the potential clinical utility of proteomic biomarkers in pediatric sepsis. Although these findings support panel-based strategies over single markers, the evidence is limited by small sample sizes, data-derived thresholds, and minimal external validation.

DISCUSSION

This systematic review summarizes evidence from four original studies to highlight the emerging role of proteomic biomarkers in the early diagnosis of pediatric sepsis. Conventional inflammatory markers, such as CRP and PCT, are still widely used in clinical practice. However, their diagnostic limitations, particularly in pediatric populations, have sparked interest in more precise, biology-driven approaches[24,25]. Proteomics enables the large-scale characterization of protein expression and regulation and has opened new avenues for understanding sepsis pathophysiology and identifying biomarkers that reflect early host-pathogen interactions, immune dysregulation, and organ dysfunction.

The included studies identified a variety of novel biomarkers, several of which demonstrated superior or complementary diagnostic performance to existing tools. IL-27, as reported by Wong *et al*[20], exhibited high specificity (92%) but moderate sensitivity (61%) for distinguishing bacterial sepsis from sterile inflammation. This makes IL-27 a valuable candidate for use in “rule-in” strategies, particularly in cases where conventional markers yield ambiguous results. Similarly, STAT3, identified by Shubin *et al*[23], achieved high sensitivity (86%) and specificity (82%), suggesting its suitability for early detection, especially given its rapid response kinetics (elevated within two to four hours of sepsis onset). These findings support the idea that targeted proteomic biomarkers may outperform traditional indicators in terms of timing and accuracy.

A recurring theme across the reviewed studies is the potential benefit of multi-marker panels. For example, Pilar-Orive *et al*[22] proposed a composite diagnostic model using sCD25, SAA1, and LRG1, which achieved an acceptable balance of sensitivity and specificity. The rationale for multiplex approaches stems from the complexity of sepsis pathophysiology, which involves the simultaneous activation of inflammatory, coagulation, and immune signaling pathways[26]. No single

Table 3 Biomarkers characteristics

Biomarker/panel	Clinical context	Platform (discovery validation)	Threshold (per study)	AUC (95%CI)	Sens	Spec	Notes
Interleukin-27	Sepsis <i>vs</i> systemic inflammatory response syndrome (diagnostic)	Transcriptomics-driven discovery to serum immunoassay	≥ 5.0 ng/mL	0.811 (0.755-0.868)	0.61	0.92	“Rule-in” behavior; outperformed PCT; classification and regression tree with PCT improved prediction
HP (infants)	Prognosis (poor outcome)	TMT-LC-MS/MS to ELISA	Study-defined	0.875 (0.700-1.000)	0.83	1.00	Opposite directionality in toddlers; age-adapted use essential
THBS1 (infants)	Prognosis (poor outcome)	TMT-LC-MS/MS to ELISA	218.38 ng/mL	0.877 (0.701-1.000)	1.00	0.60	Infant-specific signal; not significant in toddlers
HP + THBS1 (infants, combined)	Prognosis (poor outcome)	TMT-LC-MS/MS to ELISA	Panel score	0.958 (0.868-1.000)	0.917	1.00	Best infant prognostic combo
Serum amyloid A 1	Sepsis <i>vs</i> healthy (diagnostic)	Label-free LC-MS to ELISA	35891 ng/mL (Youden)	0.978 (0.946-1.000)	0.889	1.00	Early rising acute-phase protein; split patients/controls cleanly
Soluble CD25	Sepsis <i>vs</i> healthy (diagnostic)	Label-free LC-MS to ELISA	3209 pg/mL (Youden)	0.970 (0.920-1.000)	0.946	1.00	Performed better than PCT in intensive care unit admission cohorts (cited by authors)
Leucine-rich alpha-2-glycoprotein 1	Sepsis <i>vs</i> healthy (diagnostic)	Label-free LC-MS to ELISA	56951.5 ng/mL (Youden)	0.933 (0.86-1.00)	0.867	0.89	Acute-phase-responsive glycoprotein; strong single-marker ROC
Slow off-rate modified aptamer (capture reagent) signature (multi-protein)	Sepsis <i>vs</i> post-cardiopulmonary bypass infection-negative systemic inflammation (diagnostic differentiation)	SOMAscan (aptamer-based high-plex proteomic platform) 1305-plex; linear models for microarray data + Benjamini-Hochberg false-discovery-rate correction, Boruta; weighted gene co-expression network analysis	-	-	-	-	111 differentially expressed (proteins/genes) proteins (8.6% of panel); sepsis-correlated modules identified; no single-analyte ROC reported

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; ELISA: Enzyme-linked immunosorbent assays; HP: Haptoglobin; LC-MS/MS: Liquid chromatography-tandem mass spectrometry; PCT: Procalcitonin; THBS1: Thrombospondin 1; TMT: Tandem mass tags; ROC: Receiver operating characteristic.

biomarker can capture this complexity comprehensively; however, panels integrating multiple biologically relevant proteins may enhance diagnostic precision and reduce false positives or negatives[11,13]. Luo *et al*[21] also emphasized the diagnostic value of combining HP and THBS1 with SAA1/2, especially in neonates and infants, whose immune immaturity creates additional diagnostic challenges.

Importantly, this systematic review emphasized the variability in biomarker expression depending on age. Pediatric patients are a highly heterogeneous population ranging from immunologically naïve neonates to immunocompetent adolescents[27]. The maturation of the immune system affects both the host’s response to infection and the expression patterns of circulating biomarkers[6,7]. Several studies, including those by Luo *et al*[21], have addressed these age-related differences, emphasizing the need for age-adjusted reference ranges and stratification in future diagnostic frameworks. Biomarkers that perform well in adolescents may be less reliable in neonates, and *vice versa*[28,29]. This complexity must be considered in study design and clinical implementation.

The next gate is analytical validity. The platforms represented here: Slow off-rate modified aptamer (capture reagent) arrays, label-free LC-MS, TMT-LC-MS/MS, and immunoassays - have distinct pre-analytical sensitivities. The included studies emphasized early sampling, usually within a day of presentation. Ultimately, clinical laboratories will rely on validated immunoassays, making reporting of specimen handling, calibration, and between-lot stability essential[30]. Future studies should avoid data-driven thresholding, if possible, and instead establish decision limits during the development stage and verify them externally. This is because the difference between a promising receiver operating characteristic curve and a deployable test is often determined by calibration and reproducibility rather than discrimination alone.

From a clinical validity perspective, these markers are best viewed as tools that increase confidence rather than resolve uncertainty. A positive IL-27 result or a high-specificity panel result supports the use of antibiotics and source control earlier; however, a negative result should not defer treatment, but rather, inform observation, stewardship review, or timed retesting, particularly when paired with pediatric sequential organ failure assessment and the bedside trajectory [31]. The prognostic signal in infants adds granularity to early risk stratification, pointing toward tighter hemodynamic

monitoring or escalation in those at greatest risk.

None of this is exempt from the usual threats to validity. Three of the four studies were single-center, at least one relied on healthy controls, and thresholds were sometimes data-derived without external confirmation. Reference standards and blinding practices also varied. These reasons make a narrative synthesis more appropriate and honest than a meta-analysis here. The multicenter design and explicit cut-point reporting in the IL-27 study provide some counterbalance, but external validation in non-sepsis comparators with fever remains the decisive next step.

Another consideration is translating research findings into clinical practice. While some studies have utilized ELISA and CLEIA assays, which are suitable for hospital laboratories, advanced platforms such as SOMAscan or LC-MS/MS remain largely confined to research settings due to their high costs, specialized infrastructure, and the required expertise. Bridging this gap requires simplifying assay protocols, developing cost-effective platforms, and validating candidate biomarkers through regulatory approval. Furthermore, integrating proteomic tools into sepsis guidelines depends on demonstrating diagnostic accuracy and clinical utility, specifically, whether an earlier and more precise diagnosis translates into improved patient outcomes, reduced antibiotic misuse, or more tailored supportive care[32]. Our synthesis highlights the scarcity of evidence (only four studies met the inclusion criteria) and the methodological heterogeneity spanning cohort design, sampling windows, analytical platforms, and validation approaches. These factors impede reproducibility and comparability. To address these issues, we advocate for standardized pre-analytical processes, such as consistent sampling matrices and timing, platform calibration and quality assurance, prespecified thresholds, harmonized outcome definitions, and routine external validation across multiple sites.

Age-related variations

Age is a fundamental source of heterogeneity in pediatric sepsis biomarker studies. The studies enrolled children from early infancy through mid-adolescence, a period during which innate and adaptive immune functions change rapidly. Therefore, it is unsurprising that the effects of specific proteins and their clinical roles vary with age. The clearest demonstration comes from Luo *et al*[21], who compared infants (under 1 year old) and toddlers (ages 1-3) using discovery proteomics followed by ELISA validation. Pathway analyses revealed quantitative, not qualitative, differences between the two groups. Infants exhibited stronger upregulation of protein synthesis/processing and antigen presentation pathways, as well as a distinct complement activity pattern compared to toddlers. These developmental differences paralleled the clinical signal: HP, THBS1, and SAA1/2 were prognostic in infants, but not in toddlers. The HP + THBS1 combination performed best in the infant cohort (Table 3). One reasonable interpretation is that immature regulatory circuits in early life amplify specific arms of the acute-phase and endothelial/platelet responses[33]. If unchecked, this exuberant response may be associated with worse short-term outcomes[8,21].

Age-related behavior is also evident in diagnostic markers. The multicenter IL-27 study focused on children aged 10 years or younger and reported high specificity at a prespecified cut-point within the first 24 hours of presentation - a rule-in profile for that age group. Several adult studies have reported less compelling specificity for IL-27, high-lighting that performance can change with immune maturation and case mix[11,20,34]. In contrast, the Pilar-Orive *et al*'s cohort [22], which spanned from one month to 16 years, still found excellent discrimination for SAA1, LRG1, and sCD25 against healthy controls (Table 3). One plausible reason is that these proteins are involved in processes shared by both innate and adaptive immunity, such as acute-phase signaling, neutrophil/monocyte activation, and lymphocyte activation. This makes them resilient "general sepsis" signals across the pediatric age range. Nevertheless, future studies should stratify these markers by age to confirm that their thresholds and calibration remain stable in infants, school-age children, and adolescents.

Comparisons with adults and neonates further emphasize that pediatric sepsis is not merely a smaller version of the adult disease. Several markers, including SAA1 and HP, appear in both adult and pediatric proteomics; however, their timing and magnitude of change can differ. Children often mount a brisker acute-phase response, while adults may show broader overlap with non-sepsis inflammatory states[3,35]. This helps explain why IL-27, for example, appears more specific in younger cohorts than in many adult studies. Pediatric proteomics studies also tend to emphasize immune activation and complement/coagulation pathways. This reflects developmental immunology and clinical phenotypes that differ from those of adult intensive care unit populations[6,36].

Within pediatrics, neonates have distinct biology. They have impaired neutrophil chemotaxis and killing, dampened T-cell activation, immature antigen presentation, and different cytokine regulation[37]. Proteomic profiles of early-onset neonatal sepsis identify potential biomarkers such as HP, α 1-acid glycoprotein, and transferrin[38,39]. However, these proteins are influenced by prematurity, perinatal stressors (*e.g.*, hypoxia), and maternal factors. If these factors are not explicitly modeled, they can erode the biomarkers' specificity[7,10,40]. The weight of the evidence supports the independent validation of neonatal biomarkers and the establishment of age-specific reference ranges rather than the adoption of cut-points from older infants and children[2]. Given these findings, a tiered diagnostic strategy using either age-specific panels or machine-learning classifiers trained on age-stratified proteomes is the most defensible approach for achieving consistent performance across the pediatric spectrum[8,18].

This age lens also clarifies the direction of the field. Several studies show that proteomic markers can distinguish sepsis from non-sepsis earlier than conventional tests, and values obtained near presentation can correlate with severity and short-term outcomes. This enables early risk stratification[3,11,35,36]. On the other hand, there remains a gap between discovery and application. Many investigations are single-center with modest validation sets, and thresholds are sometimes data-driven. Comparator groups also do not always reflect real-world mimics that challenge clinicians, such as viral sepsis-like illness, severe inflammatory states, and postoperative systemic inflammatory response syndrome[41]. The kinetics of these proteins in children are also incompletely mapped, as most studies report only one time point. Longitudinal sampling across the first 24-48 hours would clarify optimal sampling windows, support age-adjusted cut points, and test whether these markers can monitor the response to therapy.

In practical terms, age-dependent immune ontogeny necessitates an age-stratified interpretation. Rather than pooling across the pediatric spectrum, future studies should derive developmental reference intervals and age-adjusted cut points for neonates, infants, toddlers, school-age children, and adolescents. Particular emphasis should be placed on neonatal cohorts and the feasibility of cord-blood diagnostics to capture the earliest possible diagnostic window.

Ethical and implementation considerations

The clinical implementation of proteomic biomarkers for pediatric sepsis raises important ethical and logistical considerations. Due to the vulnerability of children and the urgency of diagnosing sepsis, any new diagnostic tool must meet high safety, reproducibility, and equity standards[42,43]. Obtaining informed consent, particularly in emergency settings, can be challenging, especially when experimental biomarkers are involved. Additionally, disparities in access to advanced diagnostic technologies between high-income and low-resource settings risk exacerbating existing global inequities in pediatric care[44]. The technical complexity and high cost of platforms such as LC-MS/MS and SOMAscan hinder widespread adoption and underscore the need for simplified, point-of-care-compatible assays[45]. Aligning biomarker development with principles of clinical justice, scalability, and patient-centered care is critical for ethical translation into real-world settings. Moreover, standardizing protocols across laboratories and establishing regulatory frameworks for clinical validation is essential to ensuring the reliability, comparability, and clinical trustworthiness of proteomics-based diagnostics.

Integration of multi-omics approaches

Proteomics offers powerful insights into disease-related protein dynamics. Integrating it with other omics platforms, such as transcriptomics, metabolomics, and epigenomics, may further enhance diagnostic and prognostic capabilities in pediatric sepsis. Multi-omics approaches provide a systems-level understanding of sepsis pathophysiology by simultaneously capturing gene expression, metabolic fluxes, and protein signaling. This integrated perspective can identify converging biological signatures that more accurately reflect disease onset, progression, and resolution. For example, combining proteomic and transcriptomic data can improve identification of regulatory nodes and upstream drivers of protein-level changes. Meanwhile, metabolomics can provide real-time insight into cellular stress and immune activation [46]. Recent studies in adult sepsis have demonstrated that multi-omics models outperform single-omics approaches in predicting outcomes and guiding personalized therapies[47,48]. In pediatrics, such integration is still in its early stages, yet it shows great promise for biomarker discovery and precision medicine. Realizing this potential requires collaborative efforts to build age-specific omics datasets, harmonize analytic pipelines, and incorporate machine learning tools for integrative data interpretation.

Limitations

This systematic review has several limitations that should be acknowledged. First, the number of eligible studies was limited, and most were small-scale with heterogeneous designs and modest sample sizes. This variability reduces the generalizability of the findings and limits the ability to conduct quantitative comparisons or meta-analyses. Second, differences in study populations, such as age distribution, clinical severity, and timing of sample collection, may have introduced confounding factors that influenced biomarker expression and diagnostic performance. Third, although all studies employed validated proteomic methods, the variety of platforms and analytical processes makes direct comparisons between studies challenging and raises concerns about reproducibility. Furthermore, few studies reported on longitudinal biomarker kinetics or validated their findings in external cohorts. Publication bias is also a potential concern, as studies with negative or inconclusive results may have been underrepresented. Lastly, this systematic review focused on proteomics but did not incorporate insights from other relevant omics modalities or integrate multi-omics findings, which may further limit the scope of conclusions.

Despite these limitations, the reviewed evidence supports a growing consensus that proteomics is a powerful tool for more accurate, timely, and patient-specific diagnostics in pediatric sepsis. Future research should prioritize the multicenter, age-stratified designs with longitudinal sampling within the first 24-48 hours to define diagnostic windows and age-adjusted thresholds, as well as the incorporation of real-world comparators. Other priorities include neonatal-specific development, including cord blood, rigorous external validation, and prospective utility trials embedding parsimonious panels into bedside decision support. Integrating proteomics with other omics platforms, such as transcriptomics and metabolomics, may further refine predictive models and provide a more comprehensive understanding of sepsis biology.

CONCLUSION

Proteomics is a promising frontier in the early diagnosis and risk stratification of pediatric sepsis. It offers deeper insights into host-pathogen interactions and immune dysregulation than traditional biomarkers do. This systematic review identified several candidate proteins, such as IL-27, STAT3, HP, SAA1, and sCD25, as well as multi-marker panels that demonstrate improved diagnostic performance and response times that can be acted on clinically. These findings suggest that proteomic biomarkers could complement or surpass conventional tools, such as CRP and PCT, particularly when used in age-specific or multiplexed formats. However, despite the encouraging results, most of the identified biomarkers are still in the research phase and require rigorous validation in larger, multicenter, pediatric cohorts before they can be used in routine clinical practice. Ethical, logistical, and regulatory considerations must also be addressed to ensure equitable implementation. Future research should prioritize standardization, external validation, and the integration of

proteomics with other omics platforms to advance precision diagnostics in pediatric sepsis.

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