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Plasma proteomics in pediatric patients with sepsis– hopes and challenges

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Abstract
One of the main causes of morbidity and death in pediatric patients is sepsis. Of the 48.9 million cases of sepsis reported globally, 41.5% involve children under the age of five, with 2.9 million deaths associated with the disease. Clinicians must identify and treat patients at risk of sepsis or septic shock before late-stage organ dysfunction occurs since diagnosing sepsis in young patients is more difficult than in adult patients. As of right now, omics technologies that possess adequate diagnostic sensitivity and specificity can assist in locating biomarkers that indicate how the disease will progress clinically and how the patient will react to treatment. By identifying patients who are at a higher risk of dying or experiencing persistent organ dysfunction, risk stratification based on biomarkers generated from proteomics can enhance prognosis. A potentially helpful method for determining the proteins that serve as biomarkers for sepsis and formulating theories on the pathophysiological mechanisms behind complex sepsis symptoms is plasma proteomics.

Keywords Children, Sepsis, Proteomics

Introduction

Severe sepsis is the greatest cause of death in children and the primary reason for admission to the pediatric intensive care unit (PICU)[1]. It is estimated that among the 48.9 million sepsis cases globally, 41.5% occur in children under the age of five, with a death toll reaching up to 2.9 million[2]. Sepsis causes about 75,000 hospitalizations for children in the United States each year, as well as nearly 10,000 deaths[3]. In China, the number of deaths associated with sepsis approaches 1.03 million[4], and there are pronounced regional variations in sepsis mortality rates. In the resource-rich region of Huai'an, Jiangsu Province, the overall case fatality rate for pediatric sepsis is 3.5%[5], contrasting with a hospital mortality rate of 18.8% in the resource-constrained southwestern areas[6]. As a result, the World Health Organization (WHO) urges member states and the WHO Director-General to take concrete actions that could save millions of lives by improving prevention, diagnosis, and management to alleviate the burden of sepsis[7]. Meanwhile, the scientific community advocates for better treatment options, such as early diagnosis and proactive monitoring of high-risk hospitalized patients. Researchers are dedicated to exploring different types of biomarkers for early diagnosis of pediatric sepsis[8]. Additional biomarkers can be measured to better characterize the host's reaction to infection, allowing for more effective clinical therapy. The goal is to develop precise medical procedures for diagnosing and treating sepsis in order to increase survival rates and lessen disability caused by the infection.

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Biomarkers, as objective measures and evaluative features, serve as indicators of normal biological processes, pathological conditions, or pharmacological responses to therapeutic interventions[9] and provide references for predicting or detecting abnormalities[10]. These biomarkers may hold significant promise in disease detection and monitoring of health status, such as diagnostic, pharmacodynamic, predictive, prognostic, and surrogate[9]. Sepsis is described as a life-threatening organ malfunction caused by an abnormal host response to infection[11]. Given the complex pathophysiology of sepsis, which involves nearly all cell types, tissues, and organ systems, nearly 180 different molecules have been proposed as potential biomarkers for sepsis[12,13]. However, less than 20% of these are now utilized to diagnose sepsis[13]. Although several biomarkers exist for sepsis, none have enough specificity or sensitivity to be utilized consistently in clinical practice[13]. Biomarker research has grown significantly over the last two decades, as indicated by an increase in the number of publications. However, major efforts are still required to effectively apply these results in clinical practice.

Omics represents an emerging field that employs systems biology methodologies to gain a comprehensive understanding of biological systems. Over the past few decades, proteomics has established itself as a formidable omics tool in the medical field. The analysis of specific protein patterns in biofluids is critical for understanding pathophysiology and detecting disease indicators. Blood is frequently regarded as the most appropriate biological fluid[14]. In pediatrics, plasma proteomics has emerged as a rapidly evolving area within the field of proteomics, driven by several key factors: (1) Plasma's interaction with nearly all physiological systems renders it an exceptionally valuable biological sample for monitoring health and disease; (2) Early detection and prevention of diseases are crucial in children, as failure to address these issues may result in long-term consequences that persist throughout their lives. The analysis of the plasma/serum proteome in children with sepsis may uncover novel biomarkers associated with disease development and progression[15,16].

To date, most plasma proteomics research has predominantly focused on adults, with limited efforts directed towards establishing a comprehensive understanding of the plasma proteome in pediatric patients. Even though identifying all the proteins encoded by an organism's genome seems a daunting task, proteomics research is becoming increasingly comprehensive. As a result, current research is focusing on "omics" technologies with sufficient diagnostic specificity and sensitivity to identify biomarkers that can predict disease progression and patient response to treatment. This article reviews the pathophysiology of sepsis, provides an overview of proteomics, discusses the application of plasma proteomics in sepsis and pediatric diseases, and explores the use of plasma proteomics in pediatric sepsis.

Molecular mechanisms of sepsis pathogenesis

Activation of innate immunity

Microbial invasion causes sepsis, which occurs when pathogen-associated molecular patterns (PAMPs) produced by bacteria and damage-associated molecular patterns (DAMPs) released from damaged tissues are identified by pattern recognition receptors (PRRs) on host cell surfaces[17,18]. This identification then stimulates intracellular signaling pathways[19–22], which trigger immunological and host defense responses to local tissue injury and infection. This immunological response can be classified into three stages[18]: (1) The immediate innate response occurs within seconds to hours, characterized by the recognition of invading pathogens or tissue damage by pre-existing, non-specific or broadly specific effectors; (2) The early innate response occurs within hours to days, where the host identifies DAMPs and PAMPs, leading to the recruitment and activation of effector cells and further amplification of the inflammatory response; (3) The adaptive response occurs within days to weeks. When this response becomes excessive, it might trigger a systemic inflammatory response, causing organ dysfunction.

Immunosuppression

Experimental treatment approaches for sepsis have largely focused on blocking early inflammation or host-pathogen interactions, but these strategies have largely failed[23,24]. Research has shown that even long after the cytokine storm subsides, patients remain more susceptible to secondary infections[25], with increased viral reactivation[26,27], and immunosuppressive changes are more pronounced in patients who die from sepsis compared to survivors[28,29]. Clearly, the host immune response is disturbed in a complex way, affecting both innate and adaptive immunity. The sepsis-induced innate immune system recognizes microbes through Toll-like receptors (TLRs) and initiates a response[30]. Early activation of immune cells (monocytes/macrophages, lymphocytes, and neutrophils) is followed by a downregulation of their activity, marking the transition from an acute pro-inflammatory phase to an immunosuppressive phase, often referred to as immune paralysis[29,31,32].

Alongside the secretion of prevalent anti-inflammatory cytokines (such as IL-10), the mortality of immune cells, especially the apoptosis of T and B lymphocytes, significantly contributes to the onset of immunosuppression[33–35]. Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells with immunosuppressive functions, and DAMP activation of TLR4 can enhance MDSC accumulation[36]. MDSCs are integral

to the progression of sepsis-induced immunosuppression[37–40], with initial elevations in MDSCs facilitating the onset of hospital-acquired infections[40]. However, clinical investigations that explicitly show linkages between these alterations and clinical outcomes are still absent, and the biology of sepsis-related immunosuppression remains unclear. Consequently, there is an immediate requirement for swift, precise, and specific biomarkers to evaluate the immunological status of patients. The utilization of proteomics can assist in identifying patient subgroups with adequate homogeneity, facilitating tailored interventions with specific pharmaceuticals that alter tissue damage and particular pathways.

Pediatric versus adult sepsis

First, sepsis induces detrimental changes in the production, maturation, functionality, and apoptosis of immune cells, resulting in the dysregulation of both innate and adaptive immunological responses, characterized by excessive inflammation and immunosuppression, potentially culminating in immune paralysis. The immune response in sepsis differs markedly among patients and changes as the disease advances. Children with sepsis, akin to adults, demonstrate a simultaneous presence of pro-inflammatory and anti-inflammatory states, along with dysregulation of both innate and adaptive immune responses[41]. Children are more susceptible to immune cell imbalances than adults due to the underdevelopment of their immune systems, restricted regulatory and compensating abilities, and considerable individual variability[42,43]. While the adaptive and immunological responses of children attain levels similar to those of healthy adults by age 2, complete immune competence is not realized until puberty. Consequently, newborns and young children exhibit heightened vulnerability to serious infections caused by many pathogens, including viruses and encapsulated bacteria. Children under the age of 2 are particularly vulnerable to severe viral infections, likely attributable to diminished interferon-γ production and impaired cytotoxic lymphocyte responses, resulting in unchecked viral multiplication[44]. In comparison to adults, the disparity between inflammatory and compensatory anti-inflammatory responses may have a more significant impact on juvenile viral shock and multiple organ dysfunction syndrome (MODS). Research indicates that both adaptive and innate immune suppression occurring within the initial 48 h of viral shock in pediatric patients correlates with negative outcomes[45,46]. Clinical investigations indicate that, akin to adults, a heightened initial pro-inflammatory response in children correlates with innate immune damage, evidenced by reduced monocyte HLA-DR expression and negative infection-related outcomes[47].

Second, pediatric sepsis also has its specific clinical symptoms. The symptoms of sepsis in neonates and babies are frequently modest and may only emerge as lethargy, unwillingness to feed, or temperature instability. In contrast, older children and adults often exhibit with more typical sepsis symptoms, such as high temperature and hypotension. The progression of pediatric sepsis is fast, with considerable alterations occurring in a short period of time. Neonates and newborns are particularly prone to sudden decreases in blood pressure and respiratory failure. The clinical signs of sepsis in neonates and children can be quite mild and may be difficult to recognize. Due to the atypical symptoms, misdiagnosis as other diseases is widespread. Healthy children's circulatory systems may maintain cardiac output during prolonged severe tachycardia without generating myocardial ischemia. Children normally maintain normal blood pressure until they develop to serious cardiovascular disease, and hypotension is a late and worrisome symptom of pediatric shock[48,49]. Moreover, both children and adults may suffer sepsis-associated acute lung injury, but due to their specific anatomical and physiological characteristics, children are particularly prone to respiratory failure during critical illness. Compared with adults, young children have immature alveolar growth and poor chest wall compliance, which raises the risk of atelectasis[50]. Young children are more prone to capillary leak, left ventricular failure, and airway edema induced by inflammation. Therefore, hemodynamic treatment and respiratory ventilation assistance are particularly crucial in pediatric sepsis. Early detection of children with compensated septic shock and early intervention can avert severe decompensation that leads to mortality.

Third, juvenile septic shock has different physiological properties compared to adult septic shock. Firstly, in neonates, the detection and early management of septic shock may be hindered by the transition from fetal circulation. Increased pulmonary vascular resistance and inadequate pulmonary blood flow can hinder appropriate gas exchange, resulting to hypoxemia. Acidosis and hypoxia can further raise pulmonary vascular tone, resulting in pulmonary hypertension. This can lead to increased right ventricular afterload and cardiac failure[51]. Secondly, compared to adults, children with septic shock often display more prominent hemodynamic characteristics. Most infants with septic shock (58%) present with "cold shock," while only 20% exhibit with "warm shock"[52]. In contrast, most individuals with septic shock present with warm shock. Myocardial depression is prevalent in both pediatric and adult septic shock, although the underlying pathophysiology differs. Older patients generally demonstrate left ventricular dilatation to maintain stroke volume under stress, but neonates and babies have limited

capacity to increase stroke volume. They rely on a limited rise in heart rate to boost cardiac output in sepsis[53].

Overall, there are some connections between pediatric and adult sepsis, but there are substantial distinctions in pathogenesis, clinical presentation, and treatment options[54]. The detection and diagnosis of sepsis in juvenile patients constitute a substantial difficulty since, compared to adults, aberrant vital signs and examination results are often mild. Given the variability of sepsis as a disease state and its impact on the population, it is doubtful that a single biomarker could accurately diagnose sepsis or quantify its severity. Therefore, there is a pressing need to meaningfully screen and find novel biomarkers and to analyze the impact of new biomarkers and technologies in this field, in order to enhance the utility of these developing biomarkers in the diagnosis and management of sepsis.

The evolution of proteomics

Concept of proteomics

The term "proteome" was coined by Marc Wilkins in 1994[55]. It was originally characterized as the "protein complement of the genome". The proteome of a cell dictates its function, whereas intercellular interactions subsequently govern the physiological processes of the organism. The term "proteomics" refers to the quantitative assessment of protein levels in gene expression to elucidate biological processes, including disease mechanisms and therapeutic activities, as well as to unravel the regulatory mechanisms of gene expression[56]. Proteomics involves the examination of protein amount, size, post-translational modifications (PTMs), expression levels, localization, turnover, solubility, stability, structure, and interactions with other proteins. It delivers direct information regarding the quantity or functional status of proteins and offers insights into the structural, signaling, and enzymatic facets of the human body. Consequently, proteomics is essential for identifying critical molecules important for risk assessment, diagnosis, prognosis, disease progression prediction, therapy response, and medication development.

Development of proteomics technology

Two-dimensional gel electrophoresis (2D-GE)

2D-GE is a fundamental technique in the initial stages of proteomics research. It separates proteins by isoelectric focusing and SDS-PAGE, enabling high-resolution separation based on the isoelectric point and molecular weight of proteins. Since its inception in the mid-1970s, 2D-GE has been exploited as a quantitative tool for protein analysis. Although mass spectrometry has become the mainstream technology in proteomics, 2D gel-based proteomics still maintains distinct relevance in particular specific medical research scenarios. 2D-GE is the only proteomics technology capable of repeatedly assessing and quantifying intact proteins, offering the valuable advantage of differentiating various protein isoforms[57]. Uncontrolled protein breakdown, chemical alterations, or solubility difficulties can be easily detected through changes in the distribution of protein spots on 2D gel patterns[58]. The most prevalent and immediately visible PTMs, such as glycosylation, acetylation, phosphorylation, and deamidation, are connected with distinct cellular functions of proteins and are related to protein maintenance, energy metabolism, and cytoskeleton[59]. Therefore, the unique qualities of 2D-GE ensure its continuous utility in proteomics, allowing it to survive in niche domains, notably due to its unique capacity to function as a tool for the separation of intact proteins.

Mass spectrometry (MS)

With the increasing demand for protein analysis techniques, MS has increasingly become a crucial tool in proteomics research due to its high sensitivity and high resolution. Bottom-up shotgun proteomics is a gel-free liquid chromatography (LC)-MS approach that can detect all proteins present in a sample. Unlike gel-based proteomics, which often identifies proteins of varied abundance, LC-MS can detect all proteins that are present in the sample[60]. Currently, the bulk of proteome analyses are performed utilizing both labeled and label-free shotgun proteomics techniques[61].

Olink

Although MS-based proteomics remains the predominant approach for protein research, an emerging antibody-based proteomics technique known as Olink technology, which utilizes proximity extension assay (PEA), is gaining increasing prominence as methodologies continue to evolve. Olink technology utilizes the interaction of antibody pairs with the tertiary structure of target proteins, uniting the specificity of antibody detection with the sensitivity of polymerase chain reaction (PCR) technology. This integration is achieved through the extension of oligonucleotides by DNA polymerase[62], thereby enhancing sensitivity. By coupling target sites with paired antibody-oligonucleotide conjugates, and quantifying these known oligonucleotides via qPCR in the presence of antigens, the technique provides highly specific protein detection. The final results are presented as normalized protein eXpression (NPX) values, which are expressed in arbitrary units on a log2 scale, with higher values indicating greater protein expression.

Somalogic

Somalogic is an affinity-based technique that facilitates the scale detection of various proteins. Aptamers are short oligonucleotides engineered to specifically bind to

individual proteins, produced by introducing oligomers containing random sequences to target proteins. The target-oligomer pairs are subsequently isolated via affinity selection, and the remaining sequences are amplified. The iterative process known as systematic evolution of ligands by exponential enrichment (SELEX) enhances the specificity and affinity of the surviving oligomers for target proteins, finally discovering high-affinity single oligomers termed "aptamers." The incorporation of side chains improves the stability of these nucleic acid aptamers in biological matrices like plasma and alters their binding properties, yielding a single sequence with diverse qualities. The modified aptamers, known as Slow Off-rate Modified Aptamers (SOMAmers), can be integrated with fluorescence for multiplexing, allowing for the concurrent measurement of hundreds to thousands of proteins[63].

While enzyme-linked immunosorbent assay (ELISA) has various advantages, such as its ease of application and modest requirements for instrument performance, it has been widely employed in both clinical and research settings. However, it also has limits. For instance, changes across batches during antibody manufacture can lead to uneven outcomes. MS and Olink technologies, on the other hand, are characterized by high throughput and high sensitivity, enabling the detection of low-abundance proteins in plasma. However, MS has challenges with reproducibility, and the Olink platform is limited to known proteins only. Compared to MS and Olink technology, Somalogic technology demonstrates lower coefficients of variation (CV), greatly overcoming the inherent variability of antibody- and MS-based investigations. Nevertheless, SOMAScan requires further quantification using other methods, such as ELISA, and its SOMAmers are specific solely to the specified proteins. Additionally, the exorbitant expense of Somalogic technology precludes its broad application at present.

Plasma proteomics in sepsis

Identification of strains in bacterial/fungal co-infection samples

The utilization of peptide biomarkers alongside bottom-up proteomics (shotgun proteotyping) facilitates the identification of the predominant bacterial genera linked to sepsis (Escherichia coli, Staphylococcus aureus, and Candida) from positive cultures, exhibiting high sensitivity and precision[64]. Direct examination of patient samples depends on the effective elimination of human blood cells and plasma proteins, as these elements can obstruct the detection of bacterial and fungal pathogens, which exist at significantly lower concentrations than human-derived cells and proteins. Furthermore, proteotyping depends on the identification of distinctive peptides at any taxonomic tier, hence necessitating precise and exhaustive databases that frequently require manual curation. The misidentification of unique peptides can yield significant negative repercussions.

Through proteomic research on common bacteria that cause sepsis, it has been found[65] that exposure of isolates from four sepsis-causing pathogens to human serum produces a molecular signature of sepsis. This signature includes the acquisition of cholesterol, which has been observed across different bacterial species, along with increased fatty acid and lipid biosynthesis and metabolism. These modifications correspond with dietary adaptation for cell membrane remodeling and osmoprotection. Additionally, there is a general decrease in the abundance of proteins related to purine synthesis across all strains, indicating a reduced cell division rate. These findings provide reference data for identifying common bacterial targets for therapeutic intervention and support translational medical research. Thus, by utilizing mass spectrometry techniques, the molecular mechanisms of sepsis can be obtained from both the host and pathogen perspectives through changes in key proteins and metabolites.

Discovery of the pathophysiological molecular mechanisms of sepsis

As a branch of biotechnology study in the post-genomic era, proteomics provides the way for large-scale protein characterization. With the rapid development of proteomics technology, monitoring changes in the proteome during sepsis and identifying differentially expressed proteins help in understanding the pathophysiological processes of sepsis. Furthermore, the shift of monocytes towards aerobic glycolysis may represent a distinctive feature of clinical sepsis[66]. The impaired phagocytic function of macrophages and neutrophils, coupled with reduced human leukocyte antigen-D related (HLA-DR) expression on monocytes, are key factors contributing to immune suppression observed in sepsis[67].

Mi and colleagues[68] employed high-throughput tandem MS to delineate the plasma proteome landscape of the host response in sepsis, encompassing temporal variations, and discovered markers linked to etiology, clinical phenotypes (including organ failure), and illness severity. Significant alterations in specific proteins, co-expression modules, and networks associated with sepsis were identified, encompassing innate immunity, acute-phase response, neutrophil function, cytokine production, lipid metabolism, tissue damage protection, and extracellular matrix (ECM) organization. This extensive sepsis cohort investigation demonstrated that increased disease severity was associated with particular proteins and modules enriched in S100 family proteins and ECM proteins (positively linked), as well as complement and lipid metabolism proteins (negatively correlated). Essential proteomic

markers of distinct organ function were linked to relevant clinical acceptance criteria and overall mortality, revealing subphenotypic insights into sepsis response states, disease progression, and consequences.

A new prospective, multicenter observational cohort study[69] enrolled 363 patients with sepsis, collecting plasma samples on Day 1 and Day 4 following sepsis diagnosis for proteome analysis via mass spectrometry. The study showed a strong association between the alterations in the plasma proteome during the initial days of sepsis and mortality as well as illness severity, while pinpointing critical pathophysiological processes such as tissue injury, coagulopathy, and the activation of the complement system. By tracing the temporal changes in the plasma proteome during early sepsis, it was revealed that these changes were often related with poorer outcomes, with the innate immune system, particularly complement activation, playing a significant role in sepsis severity and death. This lays the path for future research to examine targeted therapies treating the underlying innate immune and coagulation abnormalities in sepsis, potentially improving patient outcomes.

Screening and identification of potential biomarkers for sepsis

The complexity of host responses means that no single biomarker can fully characterize or differentiate this intricacy. Over the past 20 years, numerous circulating proteins have been studied as potential alternative biomarkers for sepsis. Among these candidates, only PCT has reached the bedside in clinical trials for children[70]. The emergence of high-sensitivity and high-resolution MS technologies has enabled the identification and quantification of proteins and peptides in tissues and biological fluids, bringing new insights into disease-related processes at the molecular level[71]. By incorporating biomarkers for diagnosis, prediction, and prognosis, this experimental information can be translated into the clinical context to guide targeted therapeutic approaches. APOA2 protein has been identified as a target biomarker for H2, having a protective causal relationship with sepsis and serving as a target for H2 treatment of sepsis-related lung injury[72]. Plasma proteomics research[73] has shown that plasma lipoproteins play a crucial role in sepsis patients, complement activation leads to sepsis-associated encephalopathy, and triglyceride/cholesterol homeostasis is related to sepsis-associated acute kidney injury.

Thongboonkerd et al.[74] were the first to study changes in the sepsis plasma proteome using large animal models. They observed that early in sepsis, levels of plasma CD14, haptoglobin (an acute-phase reactant involved in oxidative stress pathways), and hemophilia proteins (anti-inflammatory molecules and oxidative scavengers) were elevated. The alterations in the plasma proteome were predominantly associated with lipoprotein metabolism, coagulation, and inflammation. A deeper understanding of the protein changes associated with organ dysfunction and sepsis-related mortality may facilitate the identification of new therapeutic targets in the future. In the plasma of sepsis patients[75], nine proteomic biomarkers were found to be associated with organ dysfunction, while twenty-two biomarkers were linked to mortality. Kapp et al. observed that the plasma proteomes in sepsis patients demonstrate molecular heterogeneity within key inflammatory pathways[76]. This molecular variability affecting survival outcomes cannot be entirely explained by socioeconomic or other non-biological factors. Recent findings have shown that bacterial sepsis and COVID-19 plasma proteins share common proteomic features and microvascular damage characteristics[77], revealing that microvascular damage is a common biological host response. Therefore, plasma proteomics could provide new insights into the pathophysiology of sepsis and ultimately offer perspectives for identifying new therapeutic targets and screening effective molecular prognostic markers for sepsis, addressing knowledge gaps in the field.

Differentiating sepsis from other diseases

Hemophagocytic lymphohistiocytosis (HLH), severe sepsis, and persistent systemic inflammatory response syndrome (SIRS) are all diseases characterized by excessive immune activation. These conditions can progress rapidly, and if not treated promptly, they carry a high risk of mortality. For children with severe sepsis, the urgent initiation of antimicrobial therapy is crucial, as delayed antibiotic treatment (even by an hour) is significantly associated with increased mortality[78]. In contrast, children with HLH require urgent immunosuppressive therapy to control high inflammation[79]. Therefore, differentiating sepsis from HLH is critical for the treatment and prognosis of affected children.

Research has found that plasma proteomics can differentiate HLH from sepsis/SIRS patients through INF-γ-regulated CXCL9 and IL-6[80]. Nicholas J. Shubin et al.[81] identified serum protein changes using an aptamer-based multiplex proteomics approach, which can be used to differentiate sepsis from non-infectious systemic inflammation. They identified 111 proteins with significantly different expression levels in serum samples from sepsis and non-infectious systemic inflammation patients on day 1. Plasma proteomics, leveraged through machine learning, can identify biomarkers such as TRIM21, PTN, and CASP8, allowing for the differentiation between COVID-19 and community-acquired pneumonia sepsis with greater accuracy than traditional clinical markers[82].

Plasma proteomics in pediatrics

Proteomics, through untargeted analysis of proteins and their forms in disease, can identify novel candidate biomarkers. In amniotic fluid proteomics analysis, neutrophil defensin-2, neutrophil defensin-1, S100A12, and S100A8 have been identified as four biomarkers indicative of intra-amniotic infection and can predict early-onset neonatal sepsis[83]. In the past two decades, with the continuous advancement of proteomics technologies, plasma proteomics has become increasingly prevalent in pediatric disease research, encompassing eleven types of conditions including inflammatory diseases, infectious diseases, respiratory disorders, hematological malignancies, cardiovascular diseases, and so on[84]. Karasawa et al.[85] employed MS-based 2DE gels proteomics during the discovery phase and ELISA for validation to search for plasma biomarkers of juvenile dermatomyositis (JDM). ELISA confirmed that the presence of specific antibodies against HSC70 could be a valuable diagnostic biomarker for JDM. In children with type I diabetes, dysregulation of islet autoimmunity-related oxidative stress proteins has been observed. Temporal expression patterns of the key antioxidative stress enzymes CAT and SOD1 suggest their potential as biomarkers for T1D[86]. In β-thalassemia patients receiving active treatment with hydroxyurea, twenty-eight biomarkers associated with erythropoietic stress and hemolysis were identified[87]. For cancer, personalized prognostic tools are critically important, as tailored therapies can significantly reduce mortality and morbidity. Proteomics can identify biomarkers associated with favorable responses to treatment in Hodgkin lymphoma, as well as detect biochemical signatures in patients with high-risk or low-risk lymphocytic leukemia[88]. Li Jieqiong and colleagues employed label-free quantitative proteomics for screening and ELISA for further validation, identifying APOC1 as a potential biomarker for rapid and non-invasive diagnosis of pediatric Mycoplasma pneumoniae (MPP)[89].

Childhood represents a unique life stage with developmentally related molecular pathways, necessitating special considerations and tailored treatments for diseases. The heterogeneity of sepsis at the individual patient level impedes progress in this field. In clinical practice, it is nearly impossible to accurately determine the onset date of sepsis. Multi-biomarker approaches and stepwise algorithms show promise in the treatment of pediatric sepsis. Previous studies have not yet identified a biomarker with sufficient sensitivity and specificity for sepsis diagnosis, but precision medicine approaches offer potential solutions for screening such heterogeneity. Proteomics, the large-scale study of protein structures and functions within cells or organisms, is a rapidly evolving field in biomedical research. It has been applied across various domains and shows significant promise in the investigation of pediatric sepsis. Plasma, interacting with nearly all physiological systems, serves as a valuable biological sample for monitoring health and disease, making it particularly suitable for studies focused on pediatric sepsis. In recent years, proteomics has been extensively used to identify biologically relevant biomarkers and generate characteristic protein profiles. Targeted proteomics analysis has revealed that a combination of multiple biomarkers (CRP, CETP, and APOA-IV) provides better diagnosis of late-onset neonatal sepsis, while three proteins involved in lipid metabolism (APOA-IV, APOC-I, and LCAT) effectively differentiate between late-onset sepsis and necrotizing enterocolitis[90].

The integration of various MS platforms (such as ion trap, orbitrap, and TOF instruments) with low or nanoflow rate liquid chromatography systems has propelled proteomics forward, enabling the detection and quantification of complex and low-abundance proteins and peptides[91,92]. Sepsis induces highly dynamic changes in the proteome and metabolome over a short period, and proteomics can precisely measure thousands of proteins and their abundances from multiple parallel samples to determine precise potential molecular mechanisms and discover personalized biomarkers and treatments. Therefore, proteomics is a potentially effective method for identifying biomarkers of sepsis and investigating the pathophysiological mechanisms of the complex sepsis syndrome[81].

The development of proteomics provides a means to study cellular processes such as cell signaling, protein modification identification, and characterization of specific biomarkers[93], as well as analysis of protein expression, localization, function, and interactions. The abundance of proteins, major isoforms, alternative splice isoforms, post-translational modifications, and protein sequence variations provide a clear snapshot of the functions of all organs in current circulation and blood contact[94].

The prospects and challenges of plasma proteomics in pediatric sepsis

Prospects

Human blood comprises tissue-specific proteins that may be discharged into the bloodstream subsequent to cellular injury or demise. The prevalence of these proteins, along with their principal isoforms, alternative splice variants, PTMs, and sequence variants, offers a distinctive overview of the present functioning condition of the circulatory system and all organs interacting with blood. For children, the ideal samples are those obtained non-invasively or minimally invasively, with blood serving as an easily accessible, broad, and sensitive diagnostic material for assessing individual and population health and disease. Several plasma proteomics studies have aimed to

identify early protein biomarkers and indicators of treatment response the pediatric patients. Human serum/plasma remains a core clinical sample for proteomics research, giving a wide pool of potential biomarkers for diverse disorders. However, the range, precision, and ease of detecting the entire protein composition, as well as the interpretation of the obtained results, remain important issues[95]. As a result, numerous potential biomarkers have been described, they have yet to be integrated into clinical practice.

Currently, key weaknesses in pediatric sepsis research include age stratification of patients, heterogeneity in treatment responses, and a lack of specific biomarkers. Significant physiological changes occur during childhood development, profoundly affecting the typical expression of nearly all proteins in plasma. The absence of reference ranges for protein expression in healthy children, coupled with limited understanding of age-specific treatment effects, hampers the effectiveness of interventions, with potential implications extending into adulthood. Plasma proteomics holds the potential to address current weaknesses in the clinical management of pediatric sepsis with precision. The application of proteomics could directly yield a set of age-specific biomarkers applicable to a wide range of disease states, thereby enhancing diagnostic efficiency and accuracy while eliminating errors associated with applying adult health ranges. This approach could pave the way for truly personalized medical care for children.

Challenges

In recent years, detection methods for protein biomarkers have progressed, markedly improving the throughput, accuracy, and sensitivity of proteomics technology. There is an increasing interest in employing advanced large-scale proteomics platforms to facilitate the development of biomarkers for the classification and risk evaluation of complicated diseases. Proteomic methodologies have been extensively utilized in the investigation of diverse pediatric disorders. Nonetheless, their utilization in illness research is still in its nascent stages. Potential biomarkers developed using proteomics encounter not only technical problems but also numerous obstacles along the translational process from the laboratory to clinical practice, including validation, clinical application, and regulatory approval.

Technological and methodological challenges

Recent breakthroughs in proteomics technologies present substantial prospects for the therapeutic utilization of biomarkers associated with pediatric sepsis. The attributes of human blood, including the extensive dynamic range of protein abundance and the remarkable diversity of the proteome, provide significant problems. The advancement of immunoaffinity depletion and diverse fractionation techniques, coupled with significant enhancements in LC-MS systems, has facilitated the investigation of the plasma proteome throughout a broad dynamic range, permitting the reliable identification of several proteins at low ng/ml concentrations. Notwithstanding these substantial advancements and endeavors, critical challenges concerning dynamic range and proteome coverage, confidence in peptide/protein identification, quantitative accuracy, analytical throughput, and the robustness of current instrumentation must be resolved prior to the routine deployment of proteomics analysis platforms appropriate for effective clinical applications[96]. The diversity, complexity, and abundance of proteins in the blood proteome render comprehensive detection by a singular method difficult, underscoring the necessity of integrating various proteomics techniques for accurate protein identification.

Furthermore, the investigation and utilization of prospective biomarkers necessitate inter-institutional data sharing and standards to guarantee data integrity and comparability. The infrastructure and policies for data sharing are essential for facilitating the translation of biomarkers[97]. Numerous biomarkers demonstrate dynamic alterations throughout the disease progression, requiring the advancement of tools for real-time monitoring of these variations. Dynamic monitoring of biomarkers is of tremendous value for determining disease progression and therapy response[98].

Challenges in biomarker validation

Biomarkers may be impacted by factors such as age, sex, genetic background, and environmental conditions, therefore making it tough to construct consistent and reproducible biomarker thresholds and signatures. Moreover, good biomarkers should display high disease specificity and sensitivity. However, many biomarkers exhibit high variation across different groups, making it challenging to meet the standards for therapeutic application. Therefore, biomarker validation is a time-consuming and costly process that requires validation across varied populations to assure consistency and reliability. While some potential biomarker detection experiments have undergone external validation and specific biomarkers have been identified, initial discoveries frequently encounter validation challenges in independent sample cohorts, including factors such as random findings, variations in sample preprocessing, or cohort biases. Additionally, validation in diverse clinical samples must be integrated with the assessment of clinical endpoints, such as disease diagnosis, disease progression, prognosis, and therapy response[98]. However, validation for clinical applicability requires long-term investigations. This may also be the reason why innovative proteomics research remains

primarily within the realm of preclinical and observational investigations.

Consequently, it is advisable to integrate biomarkers with clinical signs for a thorough evaluation to improve illness prediction efficacy. To guarantee the dependability of protein discoveries, an adequate sample size is essential, and resolving cost concerns is crucial. The exploration of multi-omics integration is significant, and improvements in bioinformatics technology are anticipated to yield insights for future integrative methodologies. The credibility of protein findings in research demands a particular sample size, and cost remains a pressing challenge to be solved.

Challenges in the translation and implementation of biomarkers

The clinical translation of biomarkers involves interdisciplinary collaboration, comprising fundamental scientists, physicians, data analysts, and regulatory bodies, among others, to promote cross-disciplinary communication and integration of resources[99]. Before entering clinical practice, sufficient scientific evidence must be provided to support their clinical utility and obtain regulatory approval, while the regulatory qualification process is complex[97]. Regulatory agencies often have long-established methods and standards predicated on animal data that may not be fully transferable to novel approaches[100].Additionally, practical application needs the design of logical clinical trials that take into consideration illness heterogeneity, patient selection, and therapy response. Beyond this, widespread use in clinical practice also requires integration with existing healthcare processes to win acceptability from physicians and patients. Therefore, we must consistently cultivate collaboration between biomarker developers and doctors to acquire the essential evidence from normal patient visits or human clinical trials.

Economic and ethical issues of biomarkers

The practical application of biomarkers needs a balance between cost and utility, particularly in healthcare settings with limited resources, to ensure their sustainability. The use of biomarkers may also create concerns regarding patient privacy and data security, especially when employing big data and artificial intelligence technology for analysis[101]. It is vital to ensure patient privacy and data security in these settings.

In summary, the translation of biomarkers from candidates to clinical practice involves complex hurdles spanning technical, clinical, economic, ethical, and regulatory aspects. These problems can be solved by interdisciplinary collaboration, technical innovation, and regulatory assistance to promote the broad application of biomarkers in disease diagnosis, treatment, and prevention.

Conclusion

The complexity and diversity of the plasma proteome present a significant challenge in developing age-specific biomarker expression profiles for diseases, with understanding protein functions adding an additional layer of complexity. Before achieving integration of proteomics, challenges such as the difficulty of conducting large-scale studies in children, the substantial sample sizes required to define reference ranges for each age group, and the efficient incorporation of this information into clinical practice must be addressed. While applying proteomics to clinical settings may take time, once results are validated, there is no reason not to incorporate proteomics into clinical practice. In summary, research into the plasma proteome of children is far from complete.

Recent breakthroughs in proteomics technology offer great prospects for the therapeutic application of biomarkers related to pediatric sepsis. New proteomics technologies provide new insights and tools for studying and treating pediatric sepsis. The integration of multi-omics is one of the important developmental directions of current proteomics technologies. By combining proteomics with other omics technologies such as genomics, transcriptomics, and metabolomics, a more comprehensive understanding of the pathophysiological mechanisms of pediatric sepsis can be achieved. By improving detection sensitivity and throughput, combining multiple technologies, and achieving multi-omics integration, these technologies not only help identify new biomarkers but also provide stronger support for the development of personalized treatment plans. In the near future, with continuing technical improvements and in-depth integration of interdisciplinary efforts, new proteomics technologies are projected to play a greater role in precision medicine for pediatric sepsis.

Author contributions

Each author is expected to have made substantial contributions to the conception OR design of the work; OR the acquisition, analysis, OR interpretation of data; OR the creation of new software used in the work; OR have drafted the work or substantively revised it. AND to have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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