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New and Traditional Biomarkers for Sepsis Diagnosis, Prognosis and Management

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Abstract

Background: Sepsis is a life-threatening condition that demands early diagnosis for effective treatment. Early diagnosis of sepsis with better markers would allow early treatment, imperative in reducing mortality and morbidity. Although numerous parameters and methods have been proposed, none fulfills all the requirements. Early detection through reliable biomarkers is crucial to reduce mortality and morbidity. An ideal method or marker of infection should be cheap, easy to measure, be highly specific and sensitive, allowing early diagnosis of sepsis, and should correlate with the severity of infection and help gauge the efficacy of the therapeutic measures.

Aims: The study aims to evaluate the current sepsis biomarkers to determine their diagnostic, prognostic, and therapeutic relevance.

Study Design: This is a narrative review of clinical trials, meta-analyses, randomized control trials and systematic reviews focusing on sepsis biomarkers.

Methods: We reviewed over 50 peer-reviewed articles on sepsis biomarkers, including studies assessing their application in clinical practice.

Results: Markers of sepsis capable of predicting the immune status of patients with sepsis may help the target population most likely to benefit from such therapies. Humoral and cellular elements of the immune response are activated

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during the immune response and induce numerous mediators and inflammatory-related molecules as cytokines, chemokines, acute phase protein and various other metabolites. Many biomarkers have been investigated, and some are now used in clinical settings to guide decision-making.

Conclusion: Sepsis is a very heterogeneous disease and there is still a long way to go on finding the ideal biomarkers, because most of these biomarkers did not pass all the steps to be introduced into clinical practice.

Keywords: Sepsis, biomarkers of sepsis, diagnosis, prognosis, therapeutic monitoring.

INTRODUCTION

Sepsis is a highly complex condition resulting from an uncontrolled host response to infection. Timely detection is essential to prevent severe outcomes and lower mortality by initiating treatment quickly. However, early diagnosis of sepsis is difficult due to the absence of distinct signs and symptoms. Thus, many efforts have been made to identify reliable biomarkers for screening patients at high risk of sepsis. Additionally, sepsis biomarkers could provide information on prognosis and guide and monitor therapy. Therefore, sepsis biomarkers represent a precious tool for clinical decision-making and for improving patient management (1). Various potential sepsis biomarkers, associated with different pathological mechanisms, have been evaluated. Sepsis begins with the activation of an innate response mediated by the detection of damage-associated molecular pattern (DAMPs) or pathogen–associated molecular patterns (PAMPs) by pattern-recognition receptors (PRRs) on host cells. In the activated immune response to sepsis, pro-inflammatory and anti-inflammatory mediators such as tumor necrosis factor –alpha (TNF –alpha), interleukin -1beta (IL1-beta), interleukins -6(IL-6) and monocyte chemoattractant- protein1(MCP-1) are released, following a rise in the levels of acute phase protein such as procalcitonin, calprotectin, pro-adrenomedullin, pentraxin-3, and C-reactive protein (CRP). In addition, the serum levels of glycoproteins on cell membrane such as presepsin, soluble triggering receptor expressed on myeloid cell1(s TREM 1), and soluble urokinase plasminogen activator receptor (suPAR) may be increased, and expression of CD64, an immunoglobulin receptor, may also be upregulated (2,3). Many of these molecules have been suggested as potential biomarkers for sepsis. In particular, procalcitonin and CRP are already widely used as biomarkers for the prediction of diagnosis and the severity of sepsis (4,5). MCP-1 is a soluble chemokine that is secreted by monocytes, endothelial cells, fibroblasts and other cells under pro-inflammatory conditions and initiates inflammatory cascade allowing the recruitment of immune cells to the site of injury. The increase in the levels of MCP-1 in sepsis patients is correlated with organ dysfunction and may help to predict a poor prognosis (6). The soluble form of TREM-1, known as sTREM-1, is primarily expressed on monocytes and neutrophils. It is crucial in sepsis, playing a key role in the inflammatory and cytotoxic responses by enhancing Toll-like receptor activation and increasing the production of pro-inflammatory cytokines (7). Several studies have demonstrated that the serum levels of sTREM1 are useful diagnostic biomarkers for sepsis (8). SuPAR, a soluble form of uPAR, is expressed on immune cells such neutrophils, lymphocytes, monocytes, and macrophages, as well as on endothelial cells, and is involved in a variety of immunological functions including cell migrations, cell adhesion, angiogenesis, fibrinolysis, and cell proliferation (9). Higher serum levels of suPAR are associated with higher mortality (10). CD 64,

a high affinity Fc gamma receptor I, is present at low levels on resting neutrophils, but its expression is up regulated in the early stages of activation of the innate immune response. The CD64 index has been suggested to be a diagnostic marker of sepsis in several studies (11,12,13). Recent advances have also led to the development of newer identified classes of biomarkers such as micro RNAs, long-non–coding RNAs, or the human microbiome. Our study represents the latest information on the biomarkers that can predict the diagnosis and prognosis of sepsis and help therapeutic decisions. This review aims to evaluate both traditional and emerging biomarkers for sepsis diagnosis and prognosis. By analyzing current literature and clinical studies, we explore the potential of these biomarkers to improve early sepsis detection, guide treatment decisions, and predict patient outcomes.

MATERIAL AND METHODS

This review focused on published clinical trials, meta-analyses, and systematic reviews evaluating sepsis biomarkers. Articles were selected based on relevance to diagnosis, prognosis, and therapeutic monitoring in sepsis. The biomarkers assessed include both traditional markers like C-reactive protein (CRP) and procalcitonin (PCT) as well as emerging biomarkers such as presepsin, soluble urokinase-type plasminogen activator receptor (suPAR), and non-coding RNAs.

RESULTS

The review analyzed over 50 peer-reviewed studies evaluating traditional and emerging biomarkers for sepsis diagnosis and prognosis. The key findings from the review are as follows:

Traditional biomarkers for sepsis diagnosis:

• CRP: Elevated in sepsis but lacks accuracy as it also increases in non-infectious inflammations and minor infections. It remains a common reference marker, though its predictive value for sepsis is limited.

• Cytokines (IL6, IL8): Elevated in sepsis, associated with severity, but have a short half-life and low specificity. High levels correlate with poor outcomes but are influenced by other conditions.

• Procalcitonin (PCT): Offers better diagnostic accuracy than CRP, especially in bacterial sepsis. Higher levels indicate severe infection and septic shock.

• SuPAR: Correlates with sepsis severity but lacks specificity in distinguishing sepsis from non-infectious inflammation.

• Neutrophil CD64: When combined with other markers like CRP, it shows high accuracy in diagnosing sepsis.

• Presepsin (CD14): Early marker with good diagnostic potential, though prognostic value is debated.

• Pentraxin-3 (PTX-3): Strong diagnostic value for sepsis, similar to PCT and IL6, and correlates with organ dysfunction.

• P-calprotectin: Promising marker with high diagnostic accuracy for sepsis, showing strong sensitivity and specificity.

• Intestinal Microbiota: Reduced diversity in sepsis patients is linked to severity, but the relationship with mortality requires further study.

Prognostic Biomarkers of Sepsis

Emerging biomarkers, such as presepsin, soluble urokinase plasminogen activator receptor (suPAR), and long non-coding RNAs, showed promise in improving the early detection and prognosis of sepsis.

In sepsis, prognostic biomarkers play a crucial role in assessing disease severity, predicting patient outcomes, and guiding treatment strategies. Here is an overview of some significant biomarkers:

1. sTREM1 (Soluble Triggering Receptor on Myeloid Cells 1): While initially showing promise as a diagnostic marker for sepsis, sTREM1 failed in larger trials. However, it has been effective in predicting mortality in septic patients at early stages of infection, including neonatal sepsis.

2. Presepsin: Presepsin levels are correlated with the SOFA score (Sequential Organ Failure Assessment) and have been proven more effective than procalcitonin (PCT) in predicting sepsis prognosis and therapeutic outcomes. It has shown significant differences in levels between survivors and non-survivors.

3. Procalcitonin (PCT): PCT is widely used as a prognostic marker, particularly in preterm infants with late neonatal sepsis. It is sensitive in detecting postoperative sepsis in children and helps identify patients at risk of sepsis-related morbidity and mortality. Studies suggest that PCT is a highly accurate biomarker for bacterial infections and has superior predictive value compared to other markers like CRP or ferritin.

4. Pentraxin-3 (PTX-3): This biomarker is associated with an increased risk of all-cause mortality in septic patients, as demonstrated by a meta-analysis. However, the heterogeneity among studies has made it difficult to establish a definitive cut-off value.

5. Cardiac Troponin: Elevated cardiac troponin levels, particularly cardiac troponin T, are linked to poor prognosis in septic patients and are associated with 30–365-day mortality post-sepsis.

6. Brain Natriuretic Peptides (BNP, NT-proBNP): These peptides, usually linked to heart failure, are elevated in septic patients and correlate with disease severity, making them useful indicators of poor prognosis.

7. Triiodothyronine (T3): Sepsis-induced stress affects endocrine function, leading to reduced T3 levels, especially in children. Low T3 is associated with worse outcomes in sepsis.

8. Adrenomedullin (ADM): ADM plays a role in regulating circulation and the inflammatory response in sepsis. The mid-regional pro-adrenomedullin (MR-proADM) fragment is more stable and correlates well with sepsis severity and mortality.

9. Ferritin: Ferritin levels are elevated during inflammation, and high serum ferritin is a

predictor of poor outcomes in sepsis, especially in children.

Emerging Biomarkers:

MicroRNAs and long non-coding RNAs have emerged as novel biomarkers, showing strong potential in predicting outcomes, but further validation is required.

1. Non-Coding RNAs (ncRNAs): miRNAs and long non-coding RNAs (lncRNAs) have shown potential as sepsis biomarkers. For instance, miR-150 correlates with immune response genes, and miR-193b has been associated with sepsis mortality.

Omics Technologies:

Genomics, transcriptomics, proteomics, and metabolomics have contributed to identifying newer biomarkers. Transcriptomics, in particular, has helped classify patients into mechanistic endotypes using RNA sequencing data. Proteomic and metabolomic approaches have identified metabolic profiles, such as fatty acids and glycerophospholipids, associated with sepsis. By integrating clinical indicators and advanced biomarkers, personalized treatment strategies can be developed, improving patient outcomes in sepsis cases.

DISCUSSION

This review highlights the evolution of sepsis biomarkers and their role in improving early detection, prognosis, and therapeutic decision-making in sepsis management.

The early diagnosis and effective management of sepsis remain critical challenges in clinical practice due to the complexity and heterogeneity of the condition. Biomarkers have become essential tools for improving diagnostic accuracy, predicting patient outcomes, and guiding therapeutic decisions. This review analyzed both traditional and emerging biomarkers, providing insights into their diagnostic and prognostic utility in sepsis.

Traditional Biomarkers

While CRP and PCT remain staples in clinical settings due to their availability and established utility, they present limitations. CRP's lack of specificity and delayed response reduces its effectiveness for timely diagnosis, while PCT's variability depending on infection type and severity can hinder its broader application in sepsis detection.

C-reactive protein (CRP) is an acute phase protein which rises early in any inflammatory response including sepsis. CRP is encoded by the CRP gene whose expression is regulated by interleukin 6(IL6) (14). A CRP concentration of <0.5 mg/dl is generally considered normal, which is typical for most healthy adults. Very high levels of CRP, >50 mg/dl, are associated with bacterial infection in 90% of cases (15). Other studies limit the usefulness as a marker of severe infection and sepsis because:

1- Plasma levels of CRP increase up to 24 hours later than those of other markers such as cytokines or PCT (16)

2- Plasma concentration of C-reactive protein may increase during minor infections and does not adequately reflect the severity of infection, nor differentiate between survivors and non-survivors of sepsis (17,18)
3- Plasma levels remain elevated for up to several days even when infection is eliminated (17)
4- CRP is also elevated during inflammatory states of non –infectious etiologies.

Probably because of these reasons, the predictive values of CRP in various patient population can be poor for the diagnosis of sepsis (19) and less so when assessing the severity of sepsis. Despite its specificity, CRP is still among the most included parameters in clinical study, and the most common markers against which most other markers have been compared to, for their diagnostic and prognostic role in sepsis.

Cytokines are peptides that regulate the amplitude and duration of the host inflammatory response (19). Cytokines are released from various cells (blood and endothelial cells, macrophage) in response to infectious stimuli and bind to the specific receptor of other cells, changing their behavior and defining their role in the inflammatory response (14). Mean serum levels of cytokines are increased in septic as compared to non-septic patients. Despite the important role cytokines play in the pathogenesis of sepsis, they do not fulfill many requirements of a good marker.

1- Some cytokines are released during sever infections and may bind to receptor antagonist, and therefore have a very short circulating half-life.
2- Cytokines are induced by numerous diseases other than sepsis or infection.
3- Assays to determine plasma cytokine levels are mostly expensive and time consuming.
4- Cytokine levels may vary or may be undetectable depending on the assay used (14)

IL6 and IL8 are most closely related to the severity and outcome of patients with sepsis (20). During sepsis, high IL6 and IL8 suggest an increased risk of complication and poor outcome (19) Furthermore, IL6 and IL8 can also be induced to a variable degree after major surgery (21) autoimmune disorders (22). Among cytokines, only IL6 and IL8 may have limited utility as a marker of the presence, severity and outcome of sepsis, because they have high sensitivity, but not high specificity.

Procalcitonin (PCT) demonstrated better diagnostic accuracy and specificity compared to CRP (23). It is now well established that its levels rise in sepsis. However, the increase of PCT is significantly influenced by the type of infection, the site of infection and the severity of disease. Higher PCT levels are seen in Gram –negative bloodstream infections (24). In burns patients has been shown to be effective for early diagnosis of sepsis (AUC: 0.92) (25). Procalcitonin levels reflect the severity of the inflammatory infectious response. PCT concentrations exceeding 10

ng/ml almost exclusively occur in patients with severe sepsis or septic shock. PCT values are of prognostic significance in patients with bacterial sepsis (26). The predictive power of procalcitonin was almost equal to that of fine needle biopsy, the gold standard (27). Dong et al (28) found in post cardiac surgery that PCT was able to identify infective SIRS compared to CRP and WBC count ($p<0.001$). Comparative studies have shown that serum PCT levels is the most diagnostically accurate biomarker for early diagnosis of sepsis caused by bacterial infection and has greater predictive value than serum ferritin, CRP, and other indicators (29). PCT when combined with CRP and IL6 significantly increased its diagnostic accuracy for sepsis (30).

SuPAR (soluble urokinase –type plasminogen activator receptor) is normally present in blood and various other body fluids and is increased in states of inflammation. In a meta-analysis by Huang et al (31) SuPAR had a moderate diagnostic ability for sepsis similar to PCT, but was inferior to PCT in differentiating from non-infective SIRS (31). Elevated suPAR is associated with mortality in patients with developed sepsis (32). SuPAR is known to indicate inflammation, regardless of etiology. Its concentrations increase in infectious diseases, malignant neoplasms, acute coronary syndromes, and other pathological conditions, correlating with the severity of the process (33).

Neutrophilic CD64 (NCD64) is a surface receptor on antigen-presenting cells that is upregulated in response to infections and endotoxin exposure. In critically ill patients, NCD64 when combined with other markers like CRP is useful for diagnosing sepsis. A normal CRP and NCD64 [(Cut-of 230 mean fluorescence intensity (MFI)] ruled out sepsis with 99% probability. An increase of >=40 MFI may indicate ICU – acquired infections in a previously non –infected patient as per their results (34).

Presepsin (CD14) is a glycoprotein that is expressed on the surface of immune cells, such as monocytes and macrophages that acts as a receptor for lipopolysaccharides (LPS). During the pro-inflammatory signaling cascade that follows exposure to infectious agents, the N-terminus of CD14 is cleaved and released into the bloodstream as soluble CD14 subtypes(35). Among these, the 13 kDa glycopeptide known as presepsin (PSEP) has been identified. Presepsin is thought to be involved in bacterial phagocytosis and the lysosomal breakdown of microorganisms. In the immune response to sepsis, the serum levels of presepsin are elevated before procalcitonin or IL6, therefore it has been proposed as a potential biomarker for the diagnosis of sepsis (36). In this study, patients with high serum presepsin levels (>=821pg/ml) had a higher mortality rate compared to patients with lower levels (33% vs.18.34% respectively) (36). These findings suggest that presepsin is a valuable diagnostic and prognostic biomarker for sepsis. Significant differences in presepsin levels were observed between sepsis patients in survival and non-survival groups. Additionally, presepsin was found to be more effective than procalcitonin

for diagnosing sepsis and differentiating bacterial infections. However, its prognostic value remains controversial in several studies (37,38).

Pentraxin -3 (PTX). Pentraxins are a type of soluble pattern recognition molecules (PRMs), which are divided into short and long pentraxins depending on the length of the N-terminal region. CRP and serum amyloid P belong to the short pentraxins, while PTX-3, PTX-4, neuronal pentraxins 1(NP1), and NP2 belong to the long pentraxins. PTX-3 is released from monocytes, dendritic cells and macrophages, epithelial cells, vascular endothelial cells, and smooth muscle cells after stimulation by toll-like receptor agonists, microbial moieties such as lipopolysaccharides or inflammatory cytokines (39). Several studies have demonstrated that PTX-3 has strong diagnostic value for sepsis. In a prospective controlled study of 213 ICU patients, PTX-3, PCT and IL6 were measured on day 1, 3 and 8 of hospitalization in sepsis patients. On each day, the diagnostic AUCs for sepsis were similarly high for PTX-3(AUC 0.92, 95%CI0.88-0.97), IL6 (AUC 0.91,95% CI0.86-0.95) and procalcitonin (AUC 0.92, 95% CI0.88-0.97). PTX-3 was also
correlated with the degree of organ disfunctions as evaluated by SOFA, APACHE II (acute physiology and chronic health evaluation) (40,41).

P- calprotectin is a heterodimeric calcium–binding protein composed of calgranulin A(S100A8) and calgranulin B (S100A9) subunits. They are expressed in a variety of cells, especially in the cytosol of myeloid cells. Calprotectin is released from activated cells after binding to cell surface receptors. It plays an important role in various cellular processes such as cell cycle progression, proliferation, differentiation, and cell survival and is involved the regulation of calcium homeostasis, zinc and manganese chelation, cytoskeletal rearrangement, cell migration, and the inhibition of microbial growth (42). Several studies have evaluated the diagnostic value of serum calprotectin levels in patients with sepsis (43). A prospective study of 125 patients demonstrated that the calprotectin AUC for predicting sepsis was as high as 0.901 (95% CI 0.852-0.942) and the sensitivity and specificity at the cut-off value of 3128.8 ng/ml were 83.15 and 88.5% respectively (44).

Intestinal microbiota is a complex community of microorganisms that exist along the gastrointestinal tract, and the intestine is the most densely and heterogeneously occupied with microorganisms among all body sites. The intestinal microbiota is crucial for maintaining human energy homeostasis, regulating intestinal endocrine function, and serving as a biosynthetic factory for vitamins and cofactors. The intestinal microbiota is also essential for the development and maturation of the immune system. It helps protect against pathogens by competing for shared nutrients, producing antimicrobial compounds, and resisting colonization (45). Several studies have demonstrated that patients with sepsis have reduced intestinal microbial

diversity compared to healthy individuals. Furthermore, a decrease in this diversity is associated with higher mortality rates among sepsis patients. However, a recent prospective cohort study on 150 patients with septic shock demonstrated that low microbial diversity was not correlated with an increase in the mortality rate (46). Further studies are required in order to understand sepsis–associated dysbiosis, which could lead to the development of biomarkers and microbiota–targeted therapies for the treatment of sepsis.

Prognostic biomarkers of sepsis

Various biomarkers like soluble triggering receptor expressed on myeloid cells 1(sTREM1), and high mobility group box1 (HMGB-1) failed to perform as diagnostic markers in larger trials (47). Some studies demonstrated that sTREM1 could also be useful in predicting mortality in septic patients at an initial stage of infection and has also been used for prognostication in neonatal septic patients (48). Presepsin in a recent prospective study, demonstrated high levels in severe sepsis correlated with SOFA score. Additionally, there was a significant difference in presepsin levels between survival and non-survival groups of sepsis patients. Presepsin was found to be a more effective biomarker than procalcitonin for assessing sepsis prognosis and evaluating therapeutic efficacy (38). Procalcitonin has a prognostic significance regarding preterm infants with late neonatal sepsis (49). PCT is a sensitive biomarker detecting postoperative sepsis in children (50), as well as in risk groups for sepsis morbidity and mortality. Comparative studies have shown that serum PCT levels are the most diagnostically accurate biomarker for early diagnosis of sepsis caused by bacterial infection and have a greater predictive value than serum ferritin, CRP, or other indicators (29).

Pentraxin-3(PTX-3) has been evaluated as a prognostic marker of sepsis. A recent meta-analysis showed that elevated PTX-3 levels were correlated with an increase of the risk of all-cause mortality (hazard ratio 1.91,95 % CI 1.53-1.56, $P<0.001$). However, in this study, the cut-of values could not be shown due to the high heterogeneity among the studies (51).

Cardiac troponin is a protein complex located on a sarcomere that regulates the interaction of myosin with actin filaments. The high sensitivity of cardiac troponin T level is a highly effective prognostic marker for lethality in patients with sepsis. It is also associated with 30–365-day mortality in survivor after the sepsis onset (52).

Brain natriuretic peptides (NPs) are cardioprotective hormones released by cardiomyocytes in response to elevated pressure or volume overload. The role of B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-pro-BNP) in the diagnosis and risk stratification of heart failure has been described. The serum level of PCT and brain NP are elevated is sepsis patients and correlate positively with the disease severity.

Therefore, they can be used as indicators of an unfavorable prognosis in sepsis patients (53).

Triiodothyronine, or T3, is an active of the thyroid of tetraiodothyronine, T4. Physical stress during sepsis can disrupt endocrine function and affect the clinical course and prognosis of the disease. In children with sepsis, the concentration of T3 in the blood serum significantly decreases. The low T3 syndrome serves as a prognostic indicator of unfavorable disease outcomes (54).

Adrenomedullin (ADM) and pro-adrenomedullin is produced mainly in endothelial cells and vascular smooth muscle cells and is involved in the regulation of systemic circulation as an autocrine /paracrine vasodilator. ADM plays a crucial role in the progression of the inflammatory response, sepsis, and septic shock. Circulating ADM is rapidly degraded and cleared from the bloodstream, making it challenging to detect with standard immunoassays due to the masking effect of its binding protein, complement factor H. The mid-regional fragment of pro-adrenomedullin (MR-pro ADM), is more stable than the ADM peptide, and its levels directly reflect the levels of the active ADM peptide (55,56). MR-pro-ADM has been identified in several studies as a prognostic marker for the prediction of mortality in sepsis and septic shock patients (56,57). A prospective observational study has been conducted to evaluate the relationship between MR-pro ADM and the severity score, such the SOFA score, the Pit (58) score, and the Clinical Pulmonary Infection Score (CPIS) (59), using linear-mixed effects models. As a result, MR-pro ADM were able to predict sepsis–related organ disfunction 24 hours before onset. This predictive role can be considered as being equivalent to a diagnostic marker for sepsis (55). A prospective study in a single center in Korea measured bio-ADM (a double monoclonal sandwich immunoassay has been developed that is able to measure C-terminally amidated biologically active ADM, bio-ADM (60) in 215 patients with sepsis and septic shock. The levels of bio-ADM in the septic shock group were significantly higher than in the sepsis group (110 vs.45.3 pg/ml, $p<0.001$), and there was a significant difference between the levels of bio-ADM in the non–survival and survival groups (137.8 vs. 55.3 pg/ml, $p<0.001$). The levels of bio-ADM also predicted 30-mortality similar to the SOFA score (AUC 0.87 vs. 0.830) (61). This marker is more effective when integrated with clinical risk indicator.

Ferritin is a protein present in most tissues. Ferritin stores iron in a mineralized, non-toxic form, but the iron within ferritin is not readily accessible for direct cellular use. Many factors, including inflammation, infection, metabolic disorders, and malignancies, can lead to increased ferritin levels in blood serum (62). The evaluation of ferritin and monocytes HLA-DR receptor expression allows the identification of sepsis patients and the assessment of the mortality risk in sepsis cases (63). It was proposed that a high serum ferritin level is an independent predictor of fatal outcomes in patients with sepsis (64). Thus, high serum levels of ferritin within five days of

the disease onset predicted unfavorable outcomes in critically ill children with severe sepsis (65). Linarez Ochoa et al. (66) conducted a comparative study in two hospitalized patient groups: those with Covid-19 and with bacterial sepsis. Ferritin was the primary inflammation marker in Covid-19 patients, while leukocytes, PCT, and D-dimer were primary markers in the patients with sepsis.

The host inflammatory response leads to the generation of products and metabolites and these have been used as the traditional biomarkers in sepsis. However new technologies are in development.

Non–coding RNAs. For decades, RNA molecules were primarily viewed as an "intermediate link" between genes and protein in the process of expressing genetic information within cells. However, the discovery that eukaryotic genes consist of protein-coding sequences interspersed with large transcribed but not translated regions of DNA paved the way for the identification of non-coding RNAs. Their roles are diverse: they regulate gene transcription and are associated with chromatin–modifying complexes: their patterns vary in different cell types, also changing in the case of diseases. By now, it has become clear that most no-coding RNAs are product of genetic loci called enhancers, which direct common effector proteins to the appropriate site to determine the fate of cells in different "life situations" (67).

MicroRNAs (miRNA), accounting for about 1% of the human genomes, but regulate up to 50% of all protein–coding genes. The biogenesis of miRNAs begins with the synthesis of primary (pre)-miRNA transcript by pre-miRNA by RNA polymerase II and III in the nucleus (68). MiRNAs are stable in a variety of body fluids and are specific to tissues or cell types and can be readily measured in a variety of ways, including by polymerase chain reaction (PCR) and microarray. MiRNAs are therefore being investigated for their potential as biomarkers in many different diseases, including cancer, neurologic disorder, cardiovascular diseases, and inflammatory diseases (69). MiRNAs are known to regulate a variety of pathways involved in the pathophysiology of sepsis, such as TLR4-mediated or pro-inflammatory cytokines-mediated pathways (70). In several studies have shown the expression level of miR-150 correlates with the expression levels of major immune response genes such as TNF alpha, IL10 and IL18 and as suggested the potential of miR:150 as a prognostic marker in patients with sepsis (71). In a prospective observational study, six mi RNAs, were identified as a prognostic marker in patients with sepsis. In particular, the AUC and multivariate odds ratio of miR;193b for the 28-day mortality rate of sepsis patients were very high, being 0.790($p<0.001$) and 9.07(95% CI 1.32-62.42) respectively, suggesting the possibility of it being a prognostic marker for sepsis (72).

Additionally, recent studies have highlighted the potential of the miR-125 family as a sepsis biomarker. This family of microRNAs has

previously been linked to the inflammatory response and organ injuries (72, 73).

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs characterized by transcripts longer than 200 nucleotides that do not contain an open reading frame. Like mRNAs, most lncRNAs are typically transcribed by RNA polymerase II. They can be classified into five different types namely, sense, antisense, intronic, intergenic, bidirectional, according to their relative position with protein coding genes and serve as decoys, scaffolds, guides, and enhancers to regulate gene expression (74). Several studies have reported that various lncRNAs are involved in the innate immune responses (75). Several studies have reported that the increase of lnc-NEAT1 (an important component of the paraspeckle structure in nuclear antibody) levels in sepsis patients was positively correlated with APACHE II and SOFA scores and associated with an unfavorable prognosis (76). Among its target mi RNAs, miR-21 is known to act as an important contributor to inflammatory responses and organ disfunction in organs such liver, kidney, and lung in sepsis (77). A recent study involving 219 sepsis patients and 219 healthy controls found that plasma levels of lnc-MEG3 and miR-21, measured within 24 hours of admission, demonstrated strong predictive value for both the diagnosis and prognosis of sepsis. (78). Although many non–coding RNAs associated with inflammatory diseases, including sepsis, have been identified, their function and mechanism are not well known and are controversial.

Omics (genomics, transcriptomics, proteomics and metabolomics) in sepsis. Omics technology, including genomics, transcriptomics, proteomics, and metabolomics are referred to as the systematic measurement at the level of DNA, RNA, protein and metabolite levels and the omics technology has led to the identification of new biomarkers for sepsis.

Genomics is the study of the genome to explain physiological or pathological processes. The variation in how individuals respond to and are susceptible to infections is influenced by genetic factors. Genomics can be used to determine genetic polymorphisms and epigenetic markers that may be used as bioindicator in septic patients (79).

Transcriptomics and proteomics have been extensively researched as tools for identifying biomarkers in sepsis. By analyzing relevant data in a molecular level, it has become possible to identify sepsis and stratify patients according to information pertaining to cellular proteins, metabolites, genes, and their expression. This allows for more homogeneous cohorts of patients that share biological similarities, which might open the door for effective treatment strategies, designed to address a certain pathophysiological pathway (80). A recent study aimed to identify novel transcriptional diagnostic and risk stratification biomarkers among ER and ICU patients from various countries worldwide with suspected infection and at least two SIRS/Sepsis

-1 criteria. Using unsupervised machine learning, several immune –related processes were found to differ among severely ill patients (24-h SOFA score), compared to patients who were less sick. Using RNA seq data, a 40-gene classification set was identified that was able to categorize patients into one of five mechanistic endotypes with an accuracy of 96% (81). Other tools that use transcriptomic data and have been developed as biomarkers for sepsis are SeptiCyte Lab (82), the sepsis mortality score (SMS) for prediction of death in septic patients (83).

The proteome refers to the complete set of proteins that a genome can produce, while the metabolome consists of all the small molecules within cells that result from both genetic activity and interactions between the genome and the environment (84). These novel analytes have been used to diagnose sepsis, reveal profiles of patients that relate to clinical outcomes, and identify future target for intervention. Techniques such as chromatography and mass-spectrometry have enabled us to study very small particles that provide information of underlying biological processes (85). In a study involving 63 critically ill patients with sepsis and 43 healthy controls, Chen et al. employed a combined proteomics and metabolomics approach to identify unique amino acid metabolism profiles that could distinguish between sepsis patients and healthy individuals. The area under the curve (AUC) values for these profiles ranged from 0.81 to 0.96. The most distinct metabolites included fatty acids, which play a role in energy production, and glycerophospholipids, which are involved in lipid signal transmission. Pathways and proteins involved in the acute inflammatory response, Toll–like receptor (TLR) signaling, defense response, and activation of myeloid cells were correlated with sepsis and sepsis- associated kidney injury (86).

A metabolomics approach has also been used to diagnose bacterial sepsis among Swedish adult ER (Emergency Room) patients (87). Of these patients, 65 had laboratory confirmed bacteremia and fulfilled the 1992 criteria for sepsis (SIRS criteria plus infection). The remaining 45 patients were initially also suspected of bacterial sepsis but were found to have negative blood cultures and laboratory–confirmed alternative diagnoses. After analyses, six metabolites were integrated into a diagnostic tool, which was tested in a subgroup of the cohort and have shown an accuracy of 88.1% (87). Metabolomics has also brought possibilities for personalizing drug treatment as was exemplified in a study in the USA in 21 patients with vasopressor-dependent septic shock treated with l-carnitine. Responder to l-carnitine had significant changes in their metabolomic signatures (88). Taken together, these data show that metabolic signatures can be used for the diagnosis of sepsis, for the stratification of patient towards a specific treatment, and as a marker of disease severity. Biomarkers are crucial not only for an early sepsis diagnosis, but also for predicting disease outcomes and optimizing treatment strategies (89).

Challenges and Future Directions

Although emerging biomarkers like presepsin, suPAR, and non-coding RNAs show potential, their widespread clinical adoption is hindered by several challenges. First, most of these biomarkers require further validation through large-scale studies before they can be integrated into routine sepsis management. Second, the lack of standardized diagnostic thresholds and assay methods limits their practical application. Lastly, sepsis is a highly heterogeneous condition, and no single biomarker is likely to provide sufficient diagnostic or prognostic information. A multimarker approach, combining traditional and novel biomarkers, may offer the best strategy for improving sepsis diagnosis and management. Such an approach would allow clinicians to account for the complexities of the disease and tailor interventions more effectively. Additionally, advancements in molecular techniques, such as transcriptomics and proteomics, could further enhance the development of personalized treatment strategies for sepsis patients.

CONCLUSION

Early diagnosis and effective management are critical to reducing sepsis mortality. However, the wide variability in symptoms among patients makes diagnosing and treating sepsis particularly challenging. Ongoing research aims to identify reliable biomarkers that can improve diagnostic accuracy and enable timely intervention, ultimately lowering the risk of death. The selection of appropriate empiric therapy can be difficult, especially with the growing problem of antibiotic resistance, often driven by irrational antibiotic use. Alongside well-established markers like suPAR, CRP, lactate, presepsin, ferritin, and PCT, highly sensitive panels have been developed for non-invasive monitoring of metabolites. Recent technological advancements have led to the discovery of promising biomarkers, including non-coding RNAs. However, further research is required to fully understand their role in sepsis pathogenesis and to develop an optimal strategy for their clinical use. Many of these new biomarkers have yet to complete the validation process required for clinical application. Given the heterogeneous nature of sepsis, finding the ideal biomarker remains a complex and ongoing challenge. A single biomarker or a panel of biomarkers holds significant potential for predicting, identifying, and developing new approaches to treat sepsis, opening new avenues for improving patient outcomes.

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