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REVIEW

Sepsis biomarkers: an omics perspective

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Abstract **Sepsis is a common cause of death in hospitalized patients worldwide. The early detection of sepsis remains a great challenge for clinicians, and delayed diagnosis frequently undermines treatment efforts, thereby contributing to high mortality. Omics technologies allow high-throughput screening of sepsis biomarkers. This review describes currently available and novel sepsis biomarkers in the context of genomics, transcriptomics, proteomics, and metabolomics. The combination of these technologies can help refine the diagnosis of sepsis. This review paper serves as a reference for future studies that employ an integrated, multi-omics approach to disease identification.**

Keywords sepsis; biomarker; genomics; transcriptomics; proteomics; metabolomics

Introduction

Sepsis is a leading cause of death among hospitalized patients worldwide. Despite recent advances in terms of management, sepsis remains a life-threatening condition with poor prognosis. The risk factors for sepsis usually include patient-related physiological characteristics, underlying diseases, or clinical treatment backgrounds. Patients with one or more of these factors are susceptible to sepsis. The most vulnerable are the elderly and infant populations; patients with chronic diseases, severe trauma, or burns; individuals who are immunocompromised or receiving immunosuppressive therapy; and malnourished and debilitated patients. The early diagnosis of sepsis is critical because mortality increases by 7.6% for each hour that appropriate antimicrobial therapy is delayed [1]. However, the accurate and timely detection of sepsis remains a great challenge because of its various nonspecific clinical manifestations and its complex and indeterminate pathophysiology. Therefore, neither microbial detection, which is considered the gold standard for identifying infection, nor traditional biomarkers can fulfill the existing need for the early diagnosis and management of sepsis [2].

Infection involves an extensive and complex pathogen-host interaction. Sepsis develops when the initial appropriate host response to an infection becomes amplified and then dysregulated [3]. The host immune defenses determine the fate of infecting organisms. That is, these organisms could remain localized; be phagocytosed and removed by immunocytes, leading to the release of pathogen components into the circulation; or multiply in local tissue and enter the bloodstream, resulting in bacteremia and sepsis. The pathogen and its structural components not only cause extensive changes in both the innate and acquired immune responses but also affect the nervous, endocrine, respiratory, circulatory, metabolic systems, etc. [3]. Traditional biomarkers for sepsis are mainly derived from this host immune/inflammatory response. Various high-throughput omics technologies facilitate comprehensive screening of sepsis-specific biomarkers. This review paper describes currently available and novel sepsis biomarkers in the context of genomics, transcriptomics, proteomics, and metabolomics to provide novel insights into the development of sepsis and ultimately offer new tools for overcoming the present diagnostic limitations.

Traditional biomarkers

Biomarkers are molecular indicators used to diagnose and predict the outcome of illnesses, as well as identify susceptible individuals. They are quantifiable measures of biological homeostasis that provide a frame of reference for identifying abnormal processes [2], and are important factors in the decision-making process of disease assessment. Commonly used biomarkers for sepsis include C-reactive

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protein (CRP) and procalcitonin (PCT) [4,5], cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-10, osteopontin] [6,7], chemokines [macrophage migration inhibitory factor (MIF), high-mobility-group box 1] [8,9], and soluble receptors [soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), soluble urokinase-type plasminogen activator receptor (suPAR)] [10,11].

The use of a single biomarker cannot satisfy all requirements for sepsis diagnosis and treatment management because sepsis has a complex pathophysiology that involves hundreds of mediators or single molecular complexes [12]. For instance, CRP is frequently used to identify infection and sepsis [2]. The plasma concentration of CRP is positively correlated with the risk of organ dysfunction and death [13,14]. However, the level of CRP cannot accurately reflect the severity of infection and sepsis because it increases during minor infection or remains high even after the time course of infection [2]. The level of CRP may also increase during an inflammatory response to noninfectious events, such as myocardial infarction, tumorigenesis, or operation. These findings suggest that CRP lacks specificity as an early-stage sepsis biomarker. By contrast, the elevation of PCT is listed as a diagnostic criterion for sepsis [15]. A recent meta-analysis that included 30 studies has revealed that PCT has a mean sensitivity of 0.77, a mean specificity of 0.79, and an area under the receiver operating characteristic curve (AUC) of 0.85 [16]. Despite its value for the early diagnosis of sepsis in critically ill patients, PCT remains unsuitable as a definitive diagnostic measure [16].

Using different combinations of biomarkers could overcome the above limitations. In a prospective cohort study of 151 patients with systemic inflammatory response syndrome (SIRS), suPAR, sTREM-1, MIF, PCT, neutrophil count, and CRP were used as biomarkers to detect the bacterial cause of inflammation, with AUCs of 0.5, 0.61, 0.63, 0.72, 0.74, and 0.81, respectively [17]. The combined AUC of the six biomarkers was determined to be 0.88 using a statistical estimation of the optimum linear combination test and the associated maximum AUC [18]. This result showed that using the six biomarkers simultaneously had better diagnostic accuracy than using any of the biomarkers alone for detecting the bacterial versus nonbacterial causes of inflammation. In another prospective study of critically ill patients [19], a bioscore that combined the polymorphonuclear neutrophil CD64 index with PCT and sTREM-1 serum levels was used to diagnose sepsis with an AUC of 0.97. This result showed that the biomarkers had better performance when used in combination than when used alone. The diagnostic accuracy of the bioscore was confirmed in a validation cohort, with 90.9% of patients being correctly classified. Although the combination of biomarkers improves diagnostic sensitivity and specificity, factors including time, cost, sample availability, and the practicability of the detection method limit the application of this approach in clinical practice.

Genomics

Genomics requires large data sets obtained from recombinant DNA methods, DNA sequencing, and bioinformatics approaches to analyze genomes and explain physiological or pathophysiological events. Similar to many pathological states, sepsis is a polygenic syndrome initiated by infection. Genetic factors determine the susceptibility and response of patients to infection [20] and can thus influence clinical outcomes [21,22]. Genomic approaches can be used to identify genetic polymorphisms and epigenetic marks that can serve as bioindicators for the detection of sepsis.

Single nucleotide polymorphisms (SNPs)

A genetic polymorphism is a regular occurrence ($> 1\%$) of two or more alleles at a given chromosome location. Several genetic polymorphisms involved in inflammation, immunity, and coagulation have been linked to sepsis susceptibility or prognosis [20]. Such polymorphisms have become the focus of most gene association studies of sepsis. SNPs, the most common type of gene polymorphism, are substitutions, deletions, or insertions of a single nucleotide occurring in approximately one of every 1000 base pairs in the human genome. SNPs could produce an altered protein, change the expression level of a normal protein, or have no discernible effect on protein function [23]. Thus, studying the SNP genotypes in sepsis is necessary to identify the potential markers of susceptibility, severity, and clinical outcome.

SNP genotyping of several genes, including CD14 [24–27], Toll-like receptors (TLRs) [22,28], lipopolysaccharide binding protein [29], cytokines [21,28,30,31], and coagulation factors [32,33], has provided information that is clinically relevant to sepsis. For example, burn patients with TLR4 and TNF-α polymorphisms are 1.8 times more likely to develop severe sepsis than patients who are homozygous; however, this increase in susceptibility is not significantly associated with mortality [28]. TLR1 SNPs are associated with increased mortality in patients with Gram-positive bacterial sepsis after traumatic injury; thus, they may serve as a novel marker for the risk of death in critically injured patients [22]. A recent study has revealed an association between the vascular endothelial growth factor + 936CC genotype and risk of developing acute kidney injury in patients with severe sepsis [30]. Genome-wide SNP genotyping assays enable the accurate detection of hundreds of thousands of SNPs in a single experiment [34,35]. Therefore, such assays are valuable to the identification of novel sepsis susceptibility-associated SNPs.

Several factors should be considered in evaluating the validity and applicability of these studies. Potential confounding variables must be identified and matched; positive association studies and replicate studies must be validated and analyzed based on the primary hypothesis rather than on

multiple comparisons; and large-scale analyses of sepsis susceptibility-associated SNP genotypes should be performed to determine new significant risk factors [20,36].

Epigenetics

Genes associated with immunity and inflammation are subject to epigenetic regulation [20], which refers to hereditary gene expression changes that are not caused by alterations in DNA sequence [37]. DNA methylation marks and histone post-translational modifications are major indicators for the epigenetic regulation of gene expression [38], and greatly impact host defense responses.

Sepsis induces epigenetic changes in dendritic cells and lymphocytes that incapacitate host defenses for an extended period after the initial immune challenge [39–41]. This late-phase immunosuppression has been confirmed in a post-mortem study [42]. Epigenetic mechanisms affect an early stage in the progression of sepsis by suppressing proinflammatory gene products and subsequent immune cell activation and proliferation. Thus, epigenetic markers can serve as biomarkers for the early diagnosis of sepsis and offer insights into the progression of this condition [43].

Transcriptomics

Gene expression

The immune response to sepsis is complex, and the exact mechanisms have yet to be fully elucidated [44]. The balance between pro- and anti-inflammatory responses is achieved through a tight regulation of gene expression [45]. Thus, evaluating the expression profiles of key genes using high-throughput DNA microarrays can reveal the immune status of septic patients. In a mouse model of sepsis, specific changes in gene expression were identified by microarray analysis of various organs and tissue, including the heart [46], liver [47], spleen [48], and leucocytes [49].

In a study of 92 intensive care unit (ICU) patients who were at risk of developing sepsis, the mRNA levels of IL-1β, IL-6, IL-8, IL-10, TNF-α, FasL, and CCL2 in the blood leukocytes were measured daily using real-time reverse transcription PCR (RT-PCR) and then analyzed with a nonlinear method (i.e., neural network analysis) [50]. The data correctly predicted the onset of sepsis in an average of 83.09% of patient cases with high sensitivity (91.43%) and selectivity (80.20%) between one and four days before a clinical diagnosis was conducted. In another study, microarray and multiplex tandem PCR were used to evaluate transcriptional profiles in circulating white blood cells of ICU septic patients, postsurgical patients, and healthy control subjects [51]. A panel of 42 gene expression markers was identified, and the prediction of sepsis from a mixed inflammatory cell population had an AUC between 86% and 92%. The gene expression profile of patients with sepsis differs from that of patients with inflammation alone, and changes in marker gene expression become apparent 0 h to 48 h prior to a clinical manifestation [52]. Therefore, changes in the expression of genes involved in innate immunity, T cell differentiation, protein synthesis, and cytokine receptor production can serve as a marker for the early diagnosis of sepsis.

Transcriptomic methods only partially reflect steady-state mRNA abundance, which is influenced by multiple factors; these methods do not provide any direct information on gene end products (proteins) and on post-translational modifications of protein function [53]. The source of RNA used in the analysis can also present a potential confounding factor. The use of whole blood as RNA source complicates gene profile analysis because of the heterogeneity of blood cell populations; meanwhile, the use of a specific cell type can result in relevant expression information from other cells being overlooked [53]. These significant shortcomings highlight the need for more reliable and clinically useful approaches.

MicroRNAs (miRNAs)

miRNAs are short RNAs of 18 to 25 nucleotides that post-transcriptionally regulate gene expression through a sequence-specific interaction with target sites in mRNA [54]. miRNAs have been linked to normal physiological and pathological processes [54]. Serum and plasma levels of miRNAs are consistent among individuals of the same species; moreover, miRNAs are resistant to RNase A digestion and remain stable even after multiple freeze-thaw cycles and long-term storage [55,56]. This stability makes miRNAs potentially useful candidates for diagnostic and other clinical applications. Although the source of circulating miRNAs is still unclear, they have been implicated in a wide range of diseases, including cancer [57,58], trauma [59,60], acute pancreatitis [61], and hepatitis [62].

Microarrays and quantitative RT-PCR were used for the genome-wide miRNA profiling of peripheral blood leukocytes and plasma of septic patients. The results demonstrated that miR-150 levels are significantly reduced in both leukocytes and plasma, and are negatively correlated with the level of disease severity as measured by the Sequential Organ Failure Assessment score, making miR-150 an early biomarker of sepsis [63]. A similar investigation on the levels of miR-150 and miR-143 in the peripheral blood leukocytes of septic patients using RT-PCR found that the expression of these miRNAs is significantly decreased and is weakly correlated with the severity of the condition. Thus, these miRNAs are useful for assessing inflammatory responses and for acting as prognostic markers of sepsis [64,65].

The pathophysiology of sepsis involves various tissue and organs. Simple screening for miRNAs differentially expressed in leukocytes excludes the mRNAs secreted by other cells that can also be contributing factors. A genome-wide microarray screen was performed to identify the serum

miRNAs that were differentially expressed in septic patients who survived and those who did not; two (miR-297 and miR-574-5p) of the identified miRNAs were further validated by RT-PCR in a larger subject group [66]. The combined assessment of serum levels, sepsis stage, and Sepsis-Related Organ Failure Assessment scores of miR-574-5p has a better predictive value than any single above-mentioned indicator for mortality. In addition, the serum levels of miR-146a and miR-223 are significantly reduced in septic patients compared with SIRS patients and healthy control subjects; therefore, these miRNAs can potentially serve as novel, highly sensitive, and specific biomarkers for sepsis [67]. Knowledge of miRNAs in the serum remains incomplete. In addition, parameters such as the expression levels of circulating miRNAs at different stages of sepsis and their potential correlation with injured organs require further investigation.

Long noncoding RNAs (lncRNAs)

In addition to DNA methylation and histone modifications, noncoding RNAs (ncRNAs) are also involved in the epigenetic control of gene expression. ncRNAs have a range of sizes and can originate from intergenic regions, introns, or enhancers [40]. Among these ncRNAs, long ncRNAs (lncRNAs) are transcripts longer than 200 nucleotides. These transcripts have widespread, differential expression in response to severe acute respiratory syndrome coronavirus infection [68], suggesting a possible link between lncRNAs and the host defense response against infection. Thus, lncRNAs can potentially become a new class of biomarkers and therapeutic targets for infectious diseases. However, future studies on the regulatory effects of lncRNAs during infection are needed.

Proteomics

The proteome is the set of all proteins that are expressed by an organism. Proteomics provides an analysis of the expression, localization, function, and interaction of proteomes. Compared with other immunologic tests, proteomics is a novel method that has the advantages of high throughput, sensitivity, and specificity. The development of proteomics has provided a means for studying cellular processes, such as cell signaling, identifying protein modifications, and characterizing specific biological markers [69].

Therefore, proteomics approaches are invaluable for clinical applications and studies of sepsis biomarkers. For instance, intravenous injection of *Pseudomonas aeruginosa* in a rabbit model of sepsis leads to the differential expression of 11 proteins in lymphocytes after 24 h, as identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. These factors are involved in the folding, assembly, transport, and degradation of proteins required for signal transmission, inflammation, immunization, energy metabolism, proliferation, differentiation, and apoptosis [70]. A recent study has established a rat model of *Acinetobacter baumannii*-induced sepsis and revealed 41 differentially expressed proteins in neutrophils using 2D electrophoresis and mass spectrometry [71]. The detected proteins include antioxidant proteins, cytoskeletal and regulatory proteins, proteins involved in signaling and energy metabolism, and proteases.

Proteomics-based analyses revealed that YKL-40 has high expression in serum samples from septic patients; thus, YKL-40 is considered a possible biomarker of sepsis [72]. Plasma profiling, which couples protein chip array with surface-enhanced laser desorption ionization time-of-flight mass spectrometry, was used to analyze the plasma of postoperative patients that had undergone liver transplantation; results revealed that five protein peaks in combination are potential diagnostic biomarkers of postoperative sepsis [73]. However, despite this promising result, the proteins have yet to be identified, and their diagnostic value must be assessed through clinical trials.

Metabolomics

Although many potential sepsis biomarkers have been identified through genomics, transcriptomics, and proteomics, the changes in cellular metabolism during sepsis cannot be ignored. Metabolomics is an emerging omics approach that focuses on metabolites with molecular weights less than 1000 kDa under physiological or pathological conditions. This approach can be used to analyze biochemical events in cells, tissue, or organs and to evaluate diseases in terms of severity. The main experimental techniques used in metabolomics include nuclear magnetic resonance (NMR), gas chromatography/mass spectrometry (GC/MS), and high performance liquid chromatography/mass spectrometry (HPLC/MS).

The development of sepsis involves the interaction of multiple systems that affect the expression levels and activities of metabolic enzymes. A more timely diagnosis and prognosis of sepsis may be achieved by detecting changes in the concentrations and ratios of metabolites [74]. A previous research identified the metabolic profiles of sera from septic rats with cecal ligation and puncture using NMR and HPLC/MS [74]. Compared with the rats that survived, those that did not survive exhibited lower levels of free fatty acids. This finding can be explained by a heightened systemic demand for energy during sepsis, suggesting that the level of free fatty acids can serve as a useful bioindicator. Moreover, an increase in the level of certain polyunsaturated fatty acids was observed; this increase can be indicative of an increased anti-inflammatory response. The metabolic profile analysis was used as a reference to develop a model for predicting outcome; this model serves as a novel tool for assessing sepsis prognosis. NMR-based metabolic profiling revealed differ-

Table 1 Potential biomarkers of sepsis from the omics technologies

Omics	Biomarkers (reference)	Methods	Patients/animals (reference)	Sensitivity (%)	Specificity (%)	Cut-off point	AUC	Changes	Clinical relevance (reference)
Genetics									
SNP	TLR1 [22]	Genotyping and logistic regression analysis	1961 trauma patients	NA	NA	NA	NA	−7202G+742A/G (Asn248Ser)	Association with increased mortality after traumatic injury and sepsis
	CD14 [24–27]	Genotyping and logistic regression analysis	14 septic patients and 30 healthy controls [24] 514 critically ill patients [25] 58 severely injured blunt trauma patients [26] 228 burn patients [27]	NA	NA	NA	NA	−260C→T	1. No association with an increased risk of severe sepsis in trauma patients [24,26] 2. Association with increased susceptibility to sepsis [27] 3. Higher −260TT genotype frequency in ICU survivor patients [25]
	IL-6, TLR4, and TNF-α [27]	Genotyping and logistic regression analysis	228 burn patients [27]	NA	NA	NA	NA	IL-6 − 174 G→C TLR4 + 896A→G TNF-α −308G→A	Association with increased risk for severe sepsis after burn injury
Transcriptomics									
Gene expression	A panel of 42 sepsis gene expression markers [51]	Affymetrix array and multiplex tandem PCR	Mixed inflammation group (28 sepsis and 38 postsurgical patients in ICU) and 20 healthy controls	NA	NA	NA	0.92	NA	A novel molecular biomarker test has the capacity for early detection of sepsis through patient monitoring
	IL-1β, IL-6, IL-8, IL-10, TNF-α, FasL and CCL2 mRNA expression [50]	qRT-PCR	92 ICU patients	91.43	80.2	NA	NA	NA	Provide a generic indicator of sepsis and help its early diagnosis
miRNAs	miR-150 [63,64]	Genome-wide miRNA profiling by microarray /qRT-PCR	17 sepsis patients and 32 healthy controls [63] 40 sepsis patients, 20 SIRS patients, and 20 health controls [64]	NA	NA	NA	NA	↓	The miR-150 levels in both leukocytes and plasma correlate with the aggressiveness and prognosis of sepsis and can be used as a marker of early diagnosis
	miR-143 [65]	qPCR	40 sepsis patients, 20 SIRS patients, and 20 healthy controls	NA	NA	NA	NA	↓	The expression level of miR-143 may be a marker for judging the severity of sepsis and its prognosis
	miR-146a [67]; miR-223 [67]	qPCR	50 sepsis patients, 30 SIRS patients, and 20 healthy controls	63.3 80	100 100	−2.98 −1.89	0.804 0.858	↓ ↓	Serum microRNAs might be used as biomarkers for early diagnosis and reflecting severity of sepsis
	miR-574-5p [66]	Genome-wide scan and qRT-PCR assay	12 surviving and 12 nonsurviving sepsis patients for microarray scan; 118 sepsis patients for validated by qRT-PCR	78.13	1.84	0.228	0.932	↓	The miR-574-5p combined with SOFA scores and sepsis stage provides a prognostic predictor of sepsis patients

(*Continued*)

Omics	Biomarkers (reference)	Methods	Patients/animals (reference)	Sensitivity (%)	Specificity (%)	Cut-off point	AUC	Changes	Clinical relevance (reference)
Proteomics	YKL-40 [72]	HPLC, SDS-PAGE; ELISA	45 sepsis or septic shock patients and 22 healthy controls and 23 patients who received off-pump coronary artery bypass grafting	NA	NA	NA	NA	↑	YKL-40 may be involved in the pathophysiology of sepsis and may be a biomarker of sepsis
Metabolomics	Acetoacetate, alanine, creatine, phosphoethanolamine, formate [75]	NMR-based metabolic profiling	14 rats underwent cecal ligation and puncture as septic group;14 rats with sham procedure as control group	100	100	NA	NA	↑(serum) ↑(serum) ↑(serum) ↓(serum)	NMR metabolomics analysis is a potentially useful technique for sepsis diagnosis
	Linoleic acid, oleic acid, stearic acid, docosahexaenoic acid, docosapentaenoic acid linolenic acid [74]	HPLC/MS assays	23 surviving and 22 nonsurviving septic rats; 25 sham-operated rats	NA	NA	NA	NA	↓(serum) ↓(serum) ↓(serum) ↑(serum) ↑(serum) ↑(serum)	A model for outcome predication was built with high sensitivity and specificity

NA: not available.

ences in metabolites of energy metabolism and inflammation in lung tissue, bronchoalveolar lavage (BAL) fluid, and serum samples obtained from septic and control rats [75]. Compared with the control rats, the septic rats had higher creatine concentration in the three samples. However, only alanine and phosphoethanolamine levels were higher in the lung tissue and serum samples of the septic rats compared with the control rats. Myo-inositol was higher in the lung tissue but lower in the BAL fluid of the septic rats compared with the control rats. In addition, the septic rats had higher acetoacetate content but lower formate content in the serum compared with the control rats. With the generation of a predictive model using partial least-squares discriminant analysis, a diagnosis of sepsis was successfully achieved using this approach.

Outlook

Sepsis involves numerous pathophysiological changes in various organ systems; thus, systematic identification of sepsis biomarkers and examination of the molecular mechanisms underlying sepsis using omics approaches may provide insights into the physiological state of patients following infection.

Several issues need to be considered before omics-based approaches can be efficiently used for the diagnosis and monitoring of sepsis in clinical settings. First, appropriate, highly specific biomarkers with high diagnostic value must be identified. The gold standard for determining infection still depends on microbial detection, which can provide a false negative result even in patients exhibiting the clinical manifestations of infection, because of the mildness of the disease, the load/type/growth capacity of pathogens, and the use of antibiotics [76]. Conversely, false positive results may be observed because of sample contamination. Therefore, perfections to this standard diagnostic method are needed.

Second, universally applicable biomarkers for sepsis, especially for multi-centered or multi-indexed investigations, are still lacking. Validation studies must be undertaken to determine the utility of diagnostic indicators; only indicators with high sensitivity, high specificity, and clinical applications should be retained.

Third, most studies of sepsis rely on a single omics approach (Table 1) rather than on a combination of omics approaches. Various omics may reveal sepsis mechanisms at different levels for a specific molecule or group of molecules; thus, a multi-pronged strategy using two or more omics can provide integrated information on particularly significant biomarkers. For instance, the Multi Analyte Pathway Inference Tool algorithm enables the principled integration of epigenomics, transcriptomics, and proteomics data for cancer diagnosis, prognosis, and biomarker discovery [77].

The lack of a clear understanding of the pathophysiology of sepsis limits biomarker identification [2]. However, the application of new technologies and the combination of multiple omics approaches are necessary to develop tools for the effective diagnosis of sepsis and to improve the prognosis for this condition.

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Compliance with ethics guidelines

Xiao Liu, Hui Ren, and Daizhi Peng declare that they have no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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