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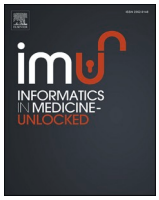

Advancing sepsis clinical research: harnessing transcriptomics for an omics-based strategy - a comprehensive scoping review

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ABSTRACT

Sepsis continues to be recognized as a significant global health challenge across all ages and is characterized by a complex pathophysiology. In this scoping review, PRISMA-ScR guidelines were adhered to, and a transcriptomic methodology was adopted, with the protocol registered on the Open Science Framework. We hypothesized that gene expression analysis could provide a foundation for establishing a clinical research framework for sepsis. A comprehensive search of the PubMed database was conducted with a particular focus on original research and systematic reviews of transcriptomic sepsis studies published between 2012 and 2022. Both coding and non-coding gene expression studies have been included in this review. An effort was made to enhance the understanding of sepsis at the mRNA gene expression level by applying a systems biology approach through transcriptomic analysis. Seven crucial components related to sepsis research were addressed in this study: endotyping (n = 64), biomarker (n = 409), definition (n = 0), diagnosis (n = 1098), progression (n = 124), severity (n =

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451), and benchmark (n = 62). These components were classified into two groups, with one focusing on Biomarkers and Endotypes and the other oriented towards clinical aspects. Our review of the selected studies revealed a compelling association between gene transcripts and clinical sepsis, reinforcing the proposed research framework. Nevertheless, challenges have arisen from the lack of consensus in the sepsis terminology employed in research studies and the absence of a comprehensive definition of sepsis. There is a gap in the alignment between the notion of sepsis as a clinical phenomenon and that of laboratory indicators. It is potentially responsible for the variable number of patients within each category. Ideally, future studies should incorporate a transcriptomic perspective. The integration of transcriptomic data with clinical endpoints holds significant potential for advancing sepsis research, facilitating a consensus-driven approach, and enabling the precision management of sepsis.

1. Introduction

Sepsis remains a significant contributor to in-hospital mortality worldwide and presents a substantial public health burden, particularly in the pediatric population [1]. In an effort to standardize sepsis management practices and emphasize early recognition and intervention, consensus guidelines have been established for both adults and children [2,3]. However, the development of protocols encounters ongoing challenges owing to gaps in clinical evidence, and a comprehensive framework for understanding sepsis remains elusive. The definition of sepsis itself has been a point of contention, with numerous iterations of adult sepsis definitions over the past decades [4,5]. The pediatric Surviving Sepsis Campaign (SSC) guidelines illustrate the consequences of an unclear definition, as they predominantly feature weak recommendations owing to the limited availability of high-quality evidence [6]. These knowledge gaps have highlighted various research priorities and unresolved pathophysiological issues. The predominant perception of sepsis as a clinical phenomenon may have constrained our understanding of its molecular foundations, potentially impeding the identification of its diagnostic and therapeutic targets. Moreover, this complicates the establishment of a universally applicable definition of sepsis across all age groups [7–9].

Despite potential therapeutic breakthroughs in sepsis, such as vitamin C [10] and activated protein-C (APC) [11], these compounds have shown limited success in clinical trials or meta-analyses. Although successful in cancer and viral infections, immunotherapy has not gained traction in bacterial sepsis, likely because of the multitude of molecular pathways resulting in sepsis-associated immune dysfunction. This slow progress in sepsis treatment underscores the gaps in our scientific knowledge [12,13] and emphasizes the critical importance of early recognition, diagnosis, and resuscitation. Furthermore, current laboratory protein biomarkers, such as CRP and procalcitonin, exhibit limited predictive capabilities [14], and the inability to stratify sepsis patients based on biochemical and immunological profiling further complicates the situation [15,16].

Sepsis poses a complex challenge owing to its multifactorial heterogeneity, resulting in variable disease processes [17]. Moreover, the transition from infection to septic shock remains poorly understood and is influenced by factors, including innate and adaptive immune mechanisms, infection severity, patient age, treatment adequacy, and genetic variability/susceptibility [18]. However, our understanding of the genetic determinants of sepsis remains limited. Additionally, the quality of clinical care provided to patients with severe infections significantly affects the natural course of the disease, particularly in children [19].

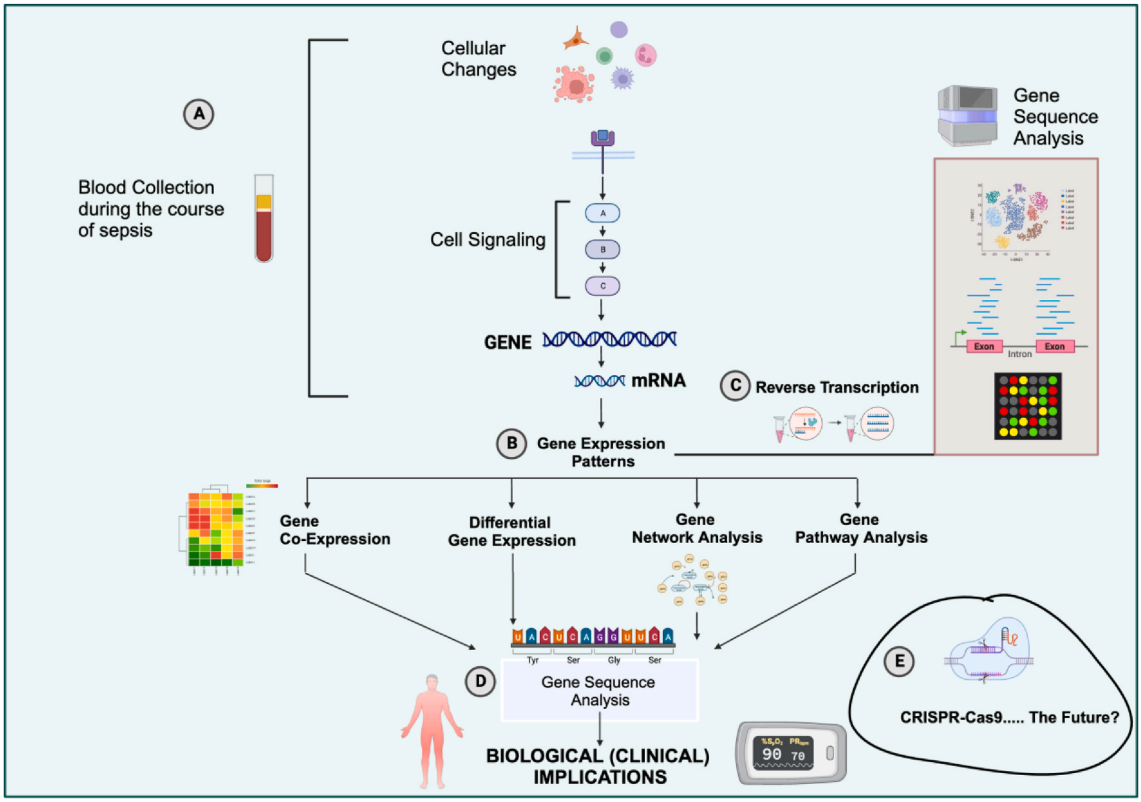

Fig. 1. Correlation between changes at the cellular level, gene expression, and bioinformatic interpretation in sepsis.

Ideally, sepsis management should be tailored to individual patient needs, considering the inherent variability among patients and external factors, such as access to healthcare services and the consistency of the quality of care delivered.

Omic approaches, including lipidomics, metabolomics, proteomics, and transcriptomics, have been employed to understand complex disease paradigms such as sepsis. Transcriptomics focuses on analyzing all RNA transcripts in a biological system, allowing the study of gene expression patterns, detection of differentially expressed genes, and description of alternative splicing events (Fig. 1). Hasson et al. (2022) highlighted the potential of transcriptomic analysis to understand sepsis-associated acute kidney injury and uncover the underlying pathophysiological mechanisms [20]. One of the key advantages of RNA-based technologies over DNA studies is their ability to reveal real-time dynamic changes for temporal understanding of sepsis. Transcriptomics offers a systems-based approach to understanding biological processes through genome-wide analysis of gene expression data [21], thereby potentially facilitating precision medicine strategies [22,23]. In this respect, enhancement of in silico techniques has facilitated system-wide gene expression analysis, contributing to a burgeoning body of knowledge.

This study aimed to explore the application of transcriptomic analysis to deepen our understanding of sepsis. This transition signifies the next step in the genetic dogma, moving from DNA to mRNA, encompassing not only the study of protein-encoding genes within coding regions of DNA, but also non-coding regions that give rise to microRNAs, circular RNA, and long non-coding RNAs.

Hence, a scoping review was undertaken to understand whether findings from transcriptomic studies can be implemented into clinical practice, particularly into international sepsis guidelines. As a part of this, the gap in the literature was also to be identified. The primary aim of this scoping review was to conduct a comprehensive analysis of peer-reviewed literature spanning a decade from 2014 to 2023, with a predominant focus on utilizing transcriptomic findings in the context of clinical sepsis. To facilitate the harmonization of research insights with gene expression studies, we introduced a framework (Fig. 2). This enhanced framework has the potential to yield significant clinical advantages, including guidance for guideline development, standardization of care pathways, and advancement of precision medicine principles. The framework presented encompasses key elements that are pivotal for establishing evidence-based sepsis guidelines. A fundamental objective was to assess whether transcriptomic studies could contribute to an enhanced understanding of sepsis committees led by peers. This study may have critical implications for the field, shedding light on gaps that could impact guidelines and clinical practices, depending on the presence of relevant research literature.

2. Materials and methods

In accordance with PRISMA-ScR guidelines [24,25], a scoping review was conducted to investigate the use of systems biology approaches to examine gene expression and its relationship with clinical sepsis. The protocol was registered on the Open Science Framework (https://osf.io/3jbv2) with the associated project osf.io/5c2wr.

2.1. Identifying the research question

This study hypothesized that transcriptional research could support a clinical research framework based on components important for sepsis guideline design. The research question posed was as follows: What gene expression studies can be used to capture relevant information for the development of sepsis guidelines concerning sepsis: definition, diagnosis, progression, severity, biomarkers, endotypes, and benchmarking?

This study incorporated gene expression investigations spanning both coding and non-coding domains. The research encapsulates micro RNA studies (<200 NBP), along with the exploration of circular (Circ)

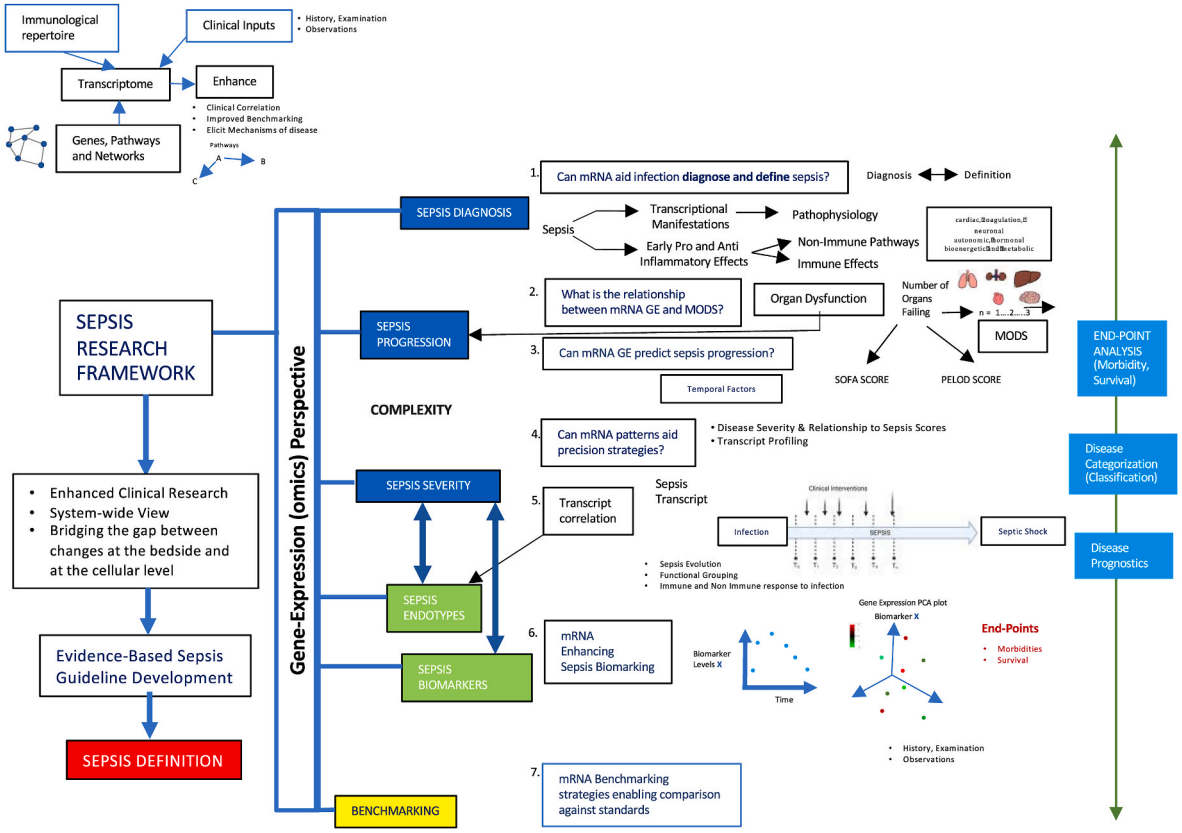

Fig. 2. Sepsis framework.

RNAs and lncRNAs.

2.2. Study selection

A systematic review of peer-reviewed literature was conducted using PubMed's online search tool, which incorporated the MEDLINE, PMC, and BookShelf databases. Relevant literature from a 10-year period leading up to the search date (June 29, 2023) was examined. The primary search terms, 'gene expression' and 'sepsis,' were utilized in conjunction with one of the thematic research terms (Endotype, Biomarker, Definitions, Diagnosis, Progression, Severity, and Benchmark) (Fig. 2 (1–7)). The search strings derived from these terms are presented in Supplementary Table 7. In the subsequent stage, articles were filtered to include human studies in English while excluding review articles and studies related to drugs and vaccines. As the key theme 'Benchmark' yielded zero selections, the filtration step was expanded beyond the title for a full article search. This modification was also applied to the 'Endotype' theme to secure a more comprehensive collection of studies.

2.3. Study inclusion and exclusion criteria

Articles were included in the review if they met the following three criteria: (i) focused on sepsis as the primary disease process and incorporated transcriptional (mRNA) analysis; (ii) addressed one of the five clinical areas of sepsis, including case definition, classification, Sepsis

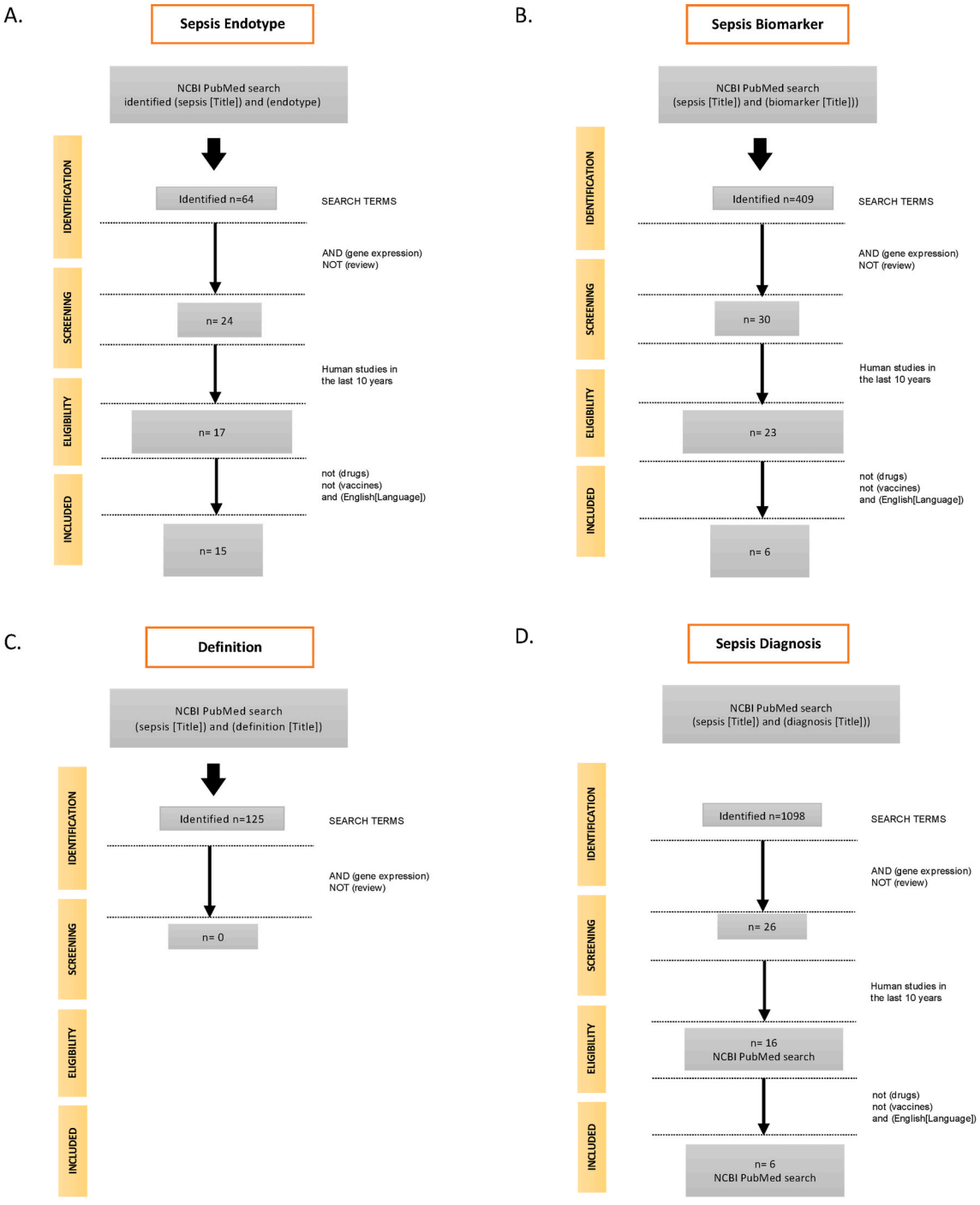

Fig. 3. Search terms.

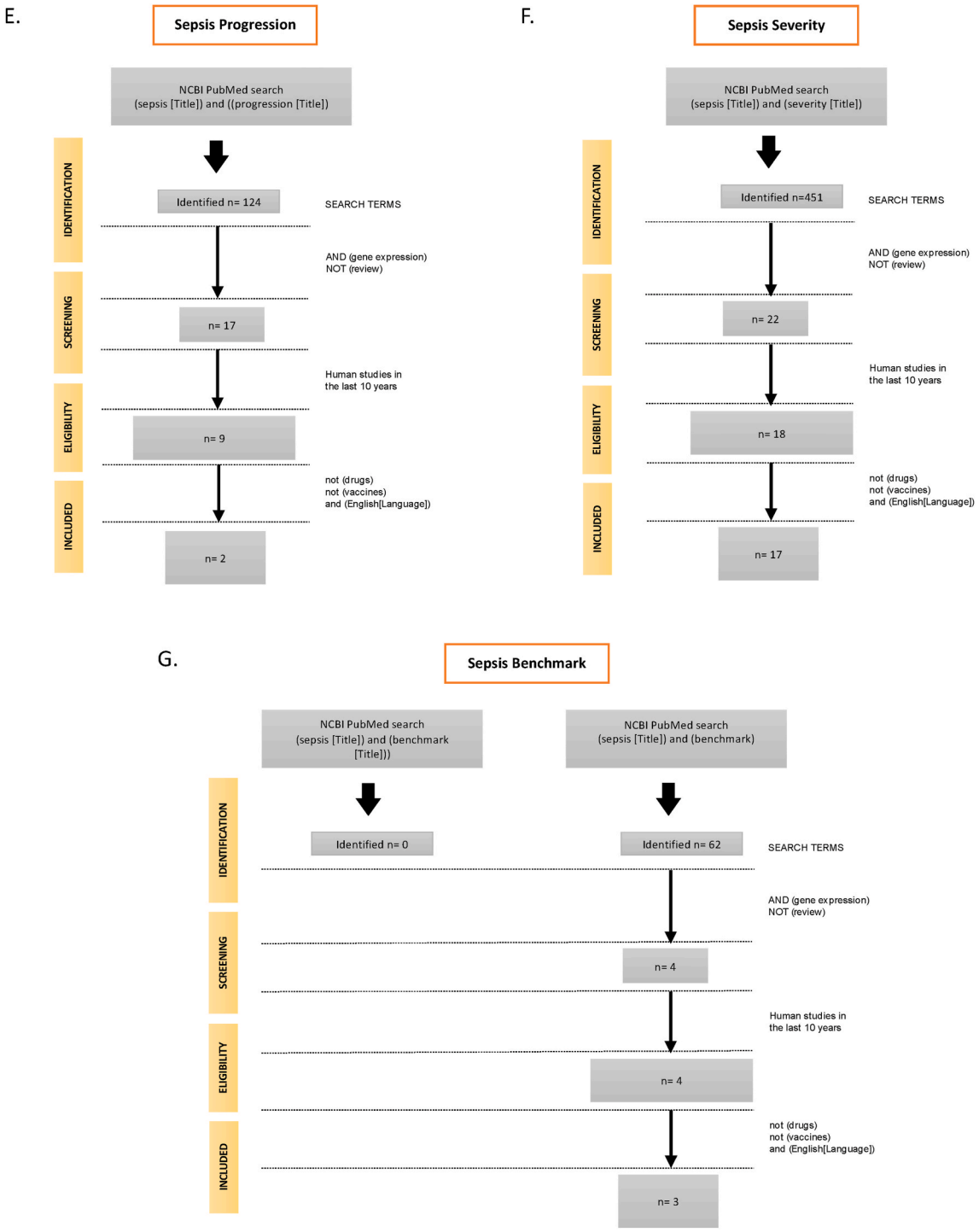

Fig. 3. (*continued*).

Severity Endotyping, Biomarkers, and Benchmarking; and (iii) involved human subjects.

The exclusion criteria were conference abstracts, articles lacking full-text access, and articles that were unavailable in English. AR and JS independently screened the articles and resolved disagreements through discussions until a consensus was reached. The articles are then detailed and discussed in the text. Relevant information regarding the application of transcript studies to sepsis was extracted and tabulated from the selected articles. The Artificial Intelligence (AI) engine 'Bing' incorporated in the Microsoft Edge browser was used to improve language and readability. (Supplementary Tables 1–6).

2.4. Data charting

We developed a data-extraction form using Microsoft Excel (AR). Two independent reviewers (AR and JS) extracted data from full-text articles to ensure consistency. The extracted data included population and study characteristics (e.g., demographics, aim, transcript information, significant genes, study outcomes, and conclusions).

2.5. Data collation and result reporting

A descriptive quantitative analysis was undertaken in this study,

involving the aggregation of articles based on keywords, in accordance with the sepsis framework mentioned earlier (Fig. 2). These studies were divided into two main categories. The first category encompasses concepts associated with cellular changes related to sepsis such as endotypes and biomarkers. The second category addressed elements that were more directly related to the clinical presentation of sepsis, including its definition, diagnosis, progression, and severity. The results are subsequently presented in this sequence, followed by a discussion of the relationship between framework terms and gene expression.

3. Results

The sepsis framework search terms identified 2333 articles (Fig. 3), which are detailed below according to the separate headings outlined in the framework search terms. A duplicate research study output occurred once with the 'Endotype' and 'Diagnosis' searches and was recorded in both these categories.

3.1. The sepsis endotype

"Endotype," derived from "endogenous phenotype," refers to disease subtypes defined by distinct biological mechanisms rather than observable symptoms. Leveraging transcriptomic analysis can identify unique endotypes, transforming sepsis diagnosis and prognosis based on the molecular characteristics and mechanisms.

Several studies have explored the association between the sepsis endotypes and mortality. Zhang et al. (2020) used deep learning, a branch of Artificial Intelligence, to identify two sepsis classes: immunosuppressed class 1 with higher mortality and relatively immunocompetent class 2 with elevated mortality risk from hydrocortisone therapy [26]. The VANISH trial found that the SRS2 endotype was associated with higher mortality when treated with corticosteroids [27]. In a study of pediatric sepsis, two endotypes (A and B) were identified, with Endotype A associated with higher 28-day mortality rates in patients with acute hypoxemic respiratory failure (AHRF) [28].

Transcriptomic analysis is invaluable for understanding the pathogenesis of sepsis. Baghela et al. (2022) accurately predicted sepsis severity and identified mechanistic endotypes in early sepsis using gene expression signatures [29]. Got et al. (2020) linked sepsis-induced Epstein-Barr virus (EBV) reactivation to an immunosuppressed host transcriptomic endotype [30]. Kwok et al. (2023) investigated neutrophils and emergency granulopoiesis in sepsis, revealing altered gene expression in circulating hematopoietic stem and progenitor cells [31]. Darden et al. (2021) used single-cell RNA sequencing to reveal the role of non-myeloid cells in chronic critical illness (CCI) and persistent inflammation, immunosuppression, and catabolism syndrome (PICS) following sepsis [32].

Combined with gene expression data, machine learning is a promising tool for identifying sepsis endotypes and for improving prognosis. Sweeney et al. (2021) classified patients into inflammatory, adaptive, and coagulopathic endotypes, which are significantly associated with clinical outcomes and can guide personalized therapy [33]. Banerjee et al. (2021) used Machine Learning to identify 20 differentially expressed genes that predict sepsis severity and outcomes [34]. Scicluna et al. (2017) identified four molecular endotypes (Mars1–4) linked to severity scores, septic shock, and mortality in patients with sepsis [35].

Endotype-based research continues to evolve, supporting the potential of personalized sepsis management. Wong et al. (2012) developed 'PERSEVERE,' a sepsis outcome prediction tool [36], while Lu et al. (2022) identified eight hub immune-related genes for sepsis diagnosis and prognosis [37]. Baghela et al. (2023) used blood sepsis gene expression signatures to predict the severity and endotypes of patients with COVID-19 [38]. They determined five endotypes that reflect distinct sepsis etiologies and therapeutic possibilities. Efforts are underway to consolidate dysregulated gene sets linked to sepsis in the form of a library, such as 'SeptiSearch,' a compendium of 103 unique gene sets developed by Baghela et al. (2023) [39]. SeptiSearch includes a description of endotypes, and is thus included in this section. Endotyping holds significant promise for advancing sepsis management and delivering personalized care to patients.

3.2. Sepsis Biomarker

Biomarkers, particularly those derived from gene expression information, are becoming increasingly essential for the diagnosis and monitoring of sepsis, offering measurable indicators of disease presence and severity. Zheng et al. (2020) differentiated between bacterial and fungal sepsis using specific gene sets, introducing the bacterial sepsis Gene Set Variation Analysis (GSVA) index, which demonstrates remarkable discriminatory power between bacterial sepsis and non-sepsis samples [40]. Furthermore, Zhang et al. (2022) emphasized the potential of Arginase 1 (ARG1) as a biomarker for diagnosing and predicting sepsis, establishing a connection between ARG1 expression, disease severity, and treatment response [41]. MicroRNAs (miRNAs) have also proven valuable in this regard, with Huang et al. (2014) identifying eight novel miRNAs associated with early sepsis diagnosis [42], and Li et al. (2022) highlighting the diagnostic and prognostic value of BCL2A1 as a novel biomarker for sepsis management [43].

In a seminal study, De Almeida et al. (2023) identified genes including Reactive Oxygen Species Modulator 1 (ROMO1), SRA Stem-Loop Interacting RNA-Binding Protein (SLIRP), and Translocase of Inner Mitochondrial Membrane 8 B (TIMM8B), which establish a connection between Non-Thyroidal Illness Syndrome (NTIS) and sepsis, offering crucial insights into shared molecular mechanisms [44]. Notably, these specific mitochondrial genes (mitGenes) have the potential to serve as biomarkers for survival prediction. These mitGenes effectively distinguished between survivors and non-survivors of sepsis, underscoring their significant role in sepsis endotyping. Among them, ROMO1, SLIRP, and TIMM8B have emerged as potential predictive biomarkers for mortality in pediatric patients with sepsis.

Transcriptomic biomarker panels are promising tools for sepsis management. Bauer et al. (2016) pioneered the development of such a panel, which effectively quantified systemic inflammation and immune dysfunction in sepsis while also distinguishing infected patients from those without infection. Notably, this panel linked a downregulated component of the genomic score to mortality [45].

3.3. Sepsis definition

Sepsis plays a pivotal role in both research and clinical findings. Sepsis plays a pivotal role in conveying The research and clinical findings. The Sepsis-3 committee recognized the complexity of aligning the clinical physiological approach with the initial immunological changes in sepsis, acknowledging that ambiguity in the definition could result in inconsistent mortality reporting [17]. In response to this challenge, the Sepsis-3 definition designates sepsis as a syndrome and acknowledges the absence of a definitive diagnostic test. Although the adult Sepsis-3 definition strives to encompass the intricacies of sepsis, it still retains an element of vagueness. While it highlights the dysregulated immunological aspects of sepsis, it does not capture intricate and complex details. A gene expression approach could be helpful in providing more depth in the definition of sepsis. For example, the transcriptomic perspective has the potential to identify functional alterations in sepsis. Schaack et al. (2018) identified distinct sepsis patient clusters exhibiting varying degrees of T-cell and monocyte functional loss along with dysregulated granulocytic neutrophil activation [46]. In addition, Reyes et al. (2020) identified 16 unique immune cell states through scRNA-seq analyses, suggesting that a transcriptomic functional interpretation of sepsis may contribute to a better understanding of its dysregulation. Nevertheless, a unifying immunological pattern that defines sepsis across various studies remains elusive [47].

The pursuit of a comprehensive definition of sepsis that encompasses

age and pathogen type is a complex endeavor. Wynn et al. (2011) proposed that age-related differences exist in septic shock, as neonates exhibit diminished gene expression in crucial immune-related pathways compared with other age groups [48]. This revelation prompts doubts regarding the viability of a universal age-independent definition. Regarding the relationship between sepsis definition and pathogen type, research on SARS-CoV-2 has underscored the parallels between bacterial sepsis and COVID-19 dysregulation mechanisms. Karakike et al. (2021) reported that most ICU-hospitalized COVID-19 patients satisfied the Sepsis-3 criteria [49]. Furthermore, the emergence of SARS-CoV-2 has redirected research focused towards viral sepsis, revealing shared features between bacterial sepsis and COVID-19 dysregulated mechanisms [50]. Additionally, Sohn et al. (2020) suggested that the immune-related transcriptome profiles of COVID-19 patients mirrored those in bacterial sepsis, advocating for a pathogen-agnostic innate host response [51]. Furthermore, Barh et al. (2020) showed that transcriptome studies of lung tissue post-SARS-CoV-2 infection revealed shared pathways among bacteria, parasites, and protozoa [52]. These findings suggest the possibility of defining pathogen-agnostic sepsis, although its actualization remains riddled with hurdles. Innovative methods, such as the transcriptomic approaches discussed in this review, might be instrumental in bridging the gap in understanding sepsis, leading to an improved definition of sepsis.

3.4. Sepsis diagnosis

Kalantar et al. (2022) conducted a study involving 221 ICU patients and discovered that host gene expression in the whole blood and plasma could accurately distinguish sepsis from non-sepsis [53]. Their approach involves machine learning to develop classifiers based on host gene expression and pathogen detection. The combination of host and microbial features significantly enhances sepsis diagnosis and allows the prediction of sepsis in patients with negative or indeterminate microbiological testing. In another study, Lukaszewski et al. (2022) identified specific gene signatures that could predict infection or sepsis three days before clinical presentation [54]. Their machine learning techniques accurately differentiated infection from uncomplicated recovery and sepsis from other postoperative presentations. Additionally, Xu et al. (2022) demonstrated that microRNAs, in combination with TLR4/TDAG8 mRNAs and proinflammatory cytokines, could serve as diagnostic biomarkers for early sepsis diagnosis [55]. Zhou et al. (2021) developed a 10-core gene expression panel for diagnosing pediatric sepsis, with the ROC showing an AUC of over 0.9 for the 10 core genes in diagnosing pediatric sepsis [56]. Recognizing the vital role of the immune system in sepsis, Lu et al. (2022) focused on immune-related genes (IRGs) and their association with sepsis diagnosis and prognosis [37]. They employed machine-learning approaches to identify hub IRGs from multiple datasets and established an IRG classifier based on eight hub IRGs. This classifier exhibited superior diagnostic efficacy and prognostic value compared with clinical characteristics alone (see the section on endotyping). The study also correlated the IRG classifier with immune-related characteristics such as immune cell infiltration and cytokine expression. Sweeney et al. (2018) validated a gene expression test known as the Sepsis Metacore (SMS) for sepsis in neonates [57]. SMS displayed accuracy in three neonatal sepsis cohorts and outperformed standard laboratory tests. This finding suggests that SMS could potentially reduce unnecessary antibiotic use and improve outcomes in neonates with sepsis.

3.5. Sepsis progression

The ability to anticipate sepsis complications early based on gene expression profiles could offer the prospect of disease modification, allowing for individualized and targeted therapies. Fiorino et al. (2022) conducted a prospective observational cohort study of 277 patients with infections, sepsis, or septic shock [58]. They used RNA sequencing of whole blood to measure the host gene expression response to infection and identify signatures that could predict sepsis progression and mortality. The researchers found no gene expression signature for sepsis progression defined by the Sepsis-3 category, but found signatures for sepsis progression defined by new organ dysfunction or ICU admission/mortality. They also validated four previously published gene signatures of sepsis-related mortality. By comparing the gene expression patterns of patients who progressed to more severe forms of sepsis or died within 28 days with those who did not, the authors identified genes and pathways associated with sepsis progression. Thus, it is possible to label sepsis progression based on host gene expression as a biomarker of host response to infection. The elicited genes and molecular pathways may reflect the different mechanisms (endotypes) of sepsis progression. The authors also used predictive modeling to generate gene expression signatures that classified patients into risk groups based on sepsis progression and mortality. Here, a molecular score was provided according to the elicited gene expression signature, complementing the clinical parameters to guide a personalized approach to clinical care. Glibetic (2022) used transcriptomic analysis to identify patient subgroups with altered biological responses to sepsis, investigating the ethnic basis of viral infection risk and sepsis progression in patients with colorectal cancer (CRC) [59]. Their analysis revealed distinct sepsis gene signatures classified as early- and late-response sepsis genes in the Native Hawaiian cohort compared to those in Japanese patients. Furthermore, canonical pathway analysis showed significant upregulation and downregulation of mechanisms related to viral exit from host cells and epithelial junction remodeling. These findings suggest that the genetic background plays a crucial role in sepsis heterogeneity, which could enable personalized approaches for risk stratification and targeted therapies.

3.6. Sepsis severity

De Jong et al. (2021) introduced an innovative method for investigating disease-associated molecular changes using gene ensemble noise [60]. This measure, which assesses the variance of gene groups, challenges the traditional gene-regulation model. The authors argued that the upregulation or downregulation of genes does not solely influence cellular dynamics, but is also affected by the stochastic nature of gene expression, which in turn affects cellular responses. This novel approach enables the detection of disruptions in pathways and protein complexes relevant to sepsis. The authors also highlighted its successful application in the context of H1N1 infection and its association with sepsis-related mortalities. Furthermore, their model could predict patient survival following sepsis and incorporate weighted gene co-expression network analysis (WGCNA), emphasizing its value in comprehending nonlinear relationships. This approach also demonstrated its ability to predict COVID-19 severity and identify potential pharmaceutical targets.

In a parallel study by Baghela et al. (2022), researchers identified gene expression patterns that could indicate sepsis severity and endotypes at the initial clinical presentation [29]. Their hypothesis revolved around the concept that sepsis encompasses various endotypes, each representing a distinct subgroup characterized by unique levels of severity and outcomes. Employing whole-blood RNA-Seq and harnessing the power of machine learning, they conducted a comprehensive analysis of gene expression profiles extracted from patients in both the emergency room (ER) and intensive care unit (ICU) with suspected sepsis. Their analysis revealed the existence of five distinct endotypes, each distinguished by its own set of underlying mechanisms. Among these endotypes, two exhibited high severity levels and increased mortality risk, whereas one displayed more benign characteristics. To facilitate early triage and potentially guide personalized treatment strategies, researchers have developed a classification tool based on a multinomial regression model enriched with LASSO shrinkage and selection operator regularization techniques. This model, which relied on 40 specific genes, demonstrated its advantages in accurately predicting

the endotype status of patients with sepsis. Consequently, this study not only illuminated the heterogeneous nature of sepsis, but also provided invaluable insights into predicting endotypes among patients with sepsis.

3.7. Sepsis benchmark

Benchmarking, the process of comparing the performance of a system or method against a recognized standard, plays a crucial role in clinical research, particularly in sepsis studies [61]. However, the core challenge is to identify the correct standard against which to benchmark it. One solution involves classifying gene patterns based on disease conditions or processes in order to create a reference library of gene patterns. Altman et al. (2021) developed a transcriptomic benchmarking framework called BloodGen3Module, designed to facilitate the analysis of gene expression data [62].

Sweeney et al. (2017) tested three gene expression diagnostic classifiers, namely the 11-gene Sepsis MetaScore, FAIM3:PLAC8 ratio, and Septicyte Lab, on 39 publicly available sepsis datasets [63]. The objective was to determine how well these classifiers could distinguish patients with infection from those with noninfectious inflammation. The three diagnostic classifiers performed similarly in separating non-infectious SIRS from sepsis, but Septicyte Lab performed less well in separating infections from healthy controls. In a subsequent study, Sweeney et al. (2018) conducted a validation study of the Sepsis MetaScore for diagnosing sepsis in neonates, demonstrating its superior performance over standard laboratory measurements across three distinct cohorts [57].

Scicluna et al. (2020) also made a significant contribution to sepsis benchmarking [64]. The authors carried out a next-generation microarray analysis of leukocyte RNA from 156 patients with sepsis and 82 healthy subjects, eight of whom underwent a lipopolysaccharide challenge in a clinically controlled setting, a process known as human endotoxemia. This study found that changes in gene expression in critically ill patients with sepsis are not exclusive to protein-coding RNAs. The expression patterns of protein-coding and long non-coding RNA profiles in sepsis closely resembled those observed in a human endotoxemia model, particularly at a specific time point associated with endotoxin tolerance. Small non-coding RNA did not demonstrate this association. Using the principles of network biology, protein-coding and non-coding RNA were grouped together as functional biological units. In sepsis, the network architecture is characterized by modules related to RNA binding, RNA biosynthesis, cell death, olfactory receptor activity, and cell-cycle G2-M DNA damage checkpoint regulation, all of which play central roles. This shows the value of using transcriptomics to understand sepsis pathogens, particularly the idea that long non-coding RNA profiles in sepsis could serve as a benchmark for future studies.

Sepsis benchmarking is an invaluable tool for the assessment and enhancement of sepsis management. Nonetheless, it is not devoid of significant challenges. One of the primary hurdles arises from the variability in the methods employed to identify patient cohorts from electronic medical record data and the clinical definitions of sepsis. This variability complicates the benchmarking process and the comparison of different methodologies [65]. Moreover, in the current era marked by the COVID-19 pandemic, accurately tracking sepsis cases presents an additional formidable challenge [66]. Furthermore, the assessment of patients with suspected sepsis is intricate, as a considerable number ultimately receive diagnoses of noninfectious conditions [67]. This complexity in diagnosis and patient categorization makes it difficult to establish meaningful benchmarks for quality indicators, particularly in the case of severe sepsis [68]. The need for well-labeled transcriptomic data and a universally accepted definition of sepsis across studies are significant hurdles. Nonetheless, sepsis benchmarking continues to be a vital tool in the evaluation of gene transcriptomic tools and methodologies, serving to guide researchers in their quest for effective prediction methods, biomarker discovery, and the development of novel therapeutics.

4. Discussion

As part of a comprehensive ten-year literature scoping review, a system-wide approach was employed, utilizing transcriptomic analysis to bridge conventional sepsis themes. This approach focuses on transcriptomics through gene expression studies across various categories, including diagnostics, organ dysfunction, sepsis severity, endotyping, classification, king, and benchmarking. As depicted in the illustrative representation of this introduced framework (Fig. 1), the interaction between scientific (biological) and clinical terms and genomic data features appears intuitive. Within the framework encompassing these terms, they are broadly categorized into two main groups. The first category offers scientific insights centered on molecular or cellular-level changes (Biomarkers and Endotypes). The second category (Sepsis Severity, Sepsis Progression, and Sepsis Diagnosis) provides a high-level perspective relevant to clinical comprehension.

Biomarkers and Endotypes offer valuable insights into sepsis (Fig. 4). The studies reviewed in this analysis demonstrated the application of Biomarkers and Endotypes in sepsis. Notably, although biomarkers have been established in sepsis research, endotyping remains a complex and evolving facet of sepsis. Biomarkers are objectively measurable entities, such as molecules in the bloodstream or changes in bodily functions that signify biological processes, pathogenic responses, or reactions to therapeutic interventions [69]. Endotypes play a pivotal role in classification by establishing a link between a disease and a distinct pathophysiological mechanism [70]. They contribute to the sub-classification of sepsis patients based on various functional criteria, employing mechanistic approaches, such as assessing the degree of immunosuppression. Research has also indicated that endotyping can identify patient groups with elevated mortality risks, with an important discovery in at-risk patients being associated with steroid therapy. This underscores the importance of applying endotypes as a facet of precision medicine. Employing endotypes can be used to predict sepsis severity and clinical outcome. Biomarkers, on the other hand, serve various purposes, such as predicting sepsis and distinguishing between bacterial and non-bacterial forms to evaluate disease severity, treatment response, and survival prognosis. They also offer the potential to quantify systemic inflammation and immune dysfunction in sepsis, thereby enabling assessment of treatment effectiveness.

Biomarkers have proven to be useful in sepsis studies, providing a convenient and objective method for disease observation, tracking, and patient response monitoring [71]. Nonetheless, endotypes could offer a more profound bridge between the biological and clinical contexts. Endotypes, representing distinct underlying disease pathways and mechanisms, are typically identified using advanced diagnostic techniques such as genetic analysis and molecular profiling. By discerning specific gene expression patterns or molecular signatures unique to a patient subgroup within a broader disease category, endotypes enable personalized treatment strategies. Continuous research and technological advancements promise to refine our understanding of endotypes, heralding the future of personalized and effective medical care.

In this study, we present a comprehensive research framework with potential clinical applicability and established essential links to critical components relevant to sepsis. A significant challenge exists within the sepsis research field, in that there is an absence of consensus regarding appropriate terminology and definitions. The components of the framework were introduced based on the researchers' clinical interpretations. The lack of consensus in terminology has likely contributed to the scarcity of studies in certain critical sepsis categories, emphasizing a central issue: the absence of a precise and universally accepted definition of sepsis. This inherent ambiguity is a limitation of the present study, stemming from the blurred boundaries between research terminologies, especially concerning clinical descriptors, such as sepsis severity and progression. Furthermore, there is a considerable

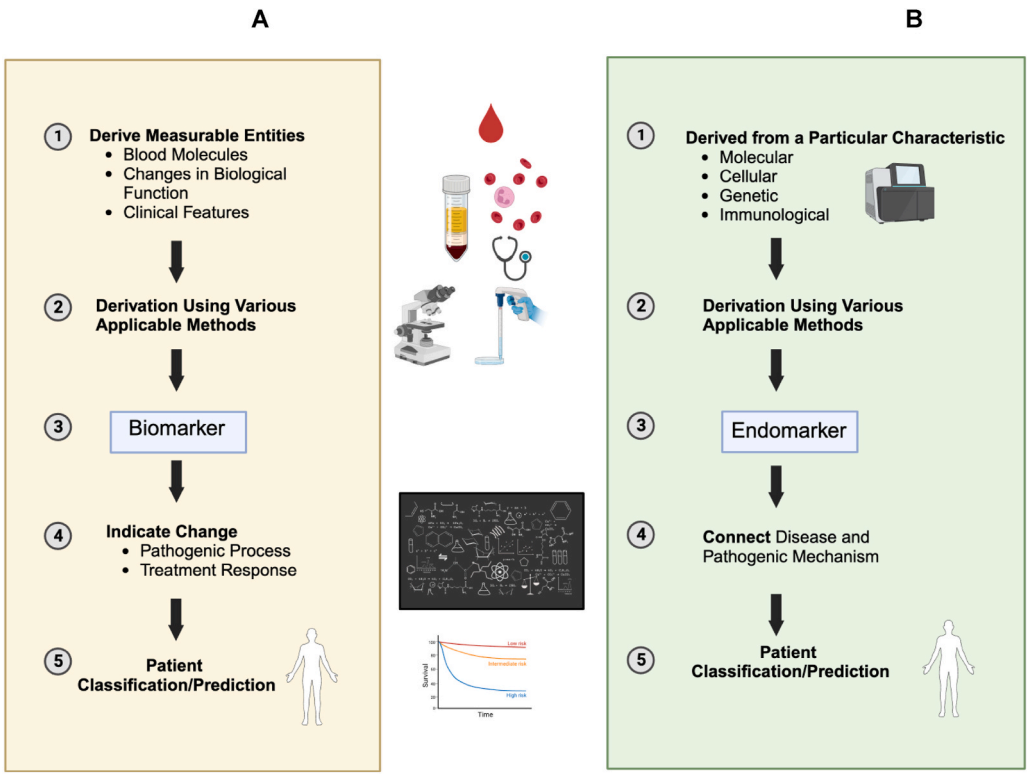

Fig. 4. Biomarkers Change Quantifiers and Endomarkers as Patient Classifiers, as applied to Sepsis.

gap between the wealth of scientific insights into sepsis and its practical clinical applications. This gap is exacerbated by the complexities inherent in sepsis research, including platform heterogeneity, challenges related to the timing of sample collection, and variations arising from host-pathogen interactions(Fig. 5). These intricacies pose significant barriers to seamlessly integrating the findings from diverse sepsis

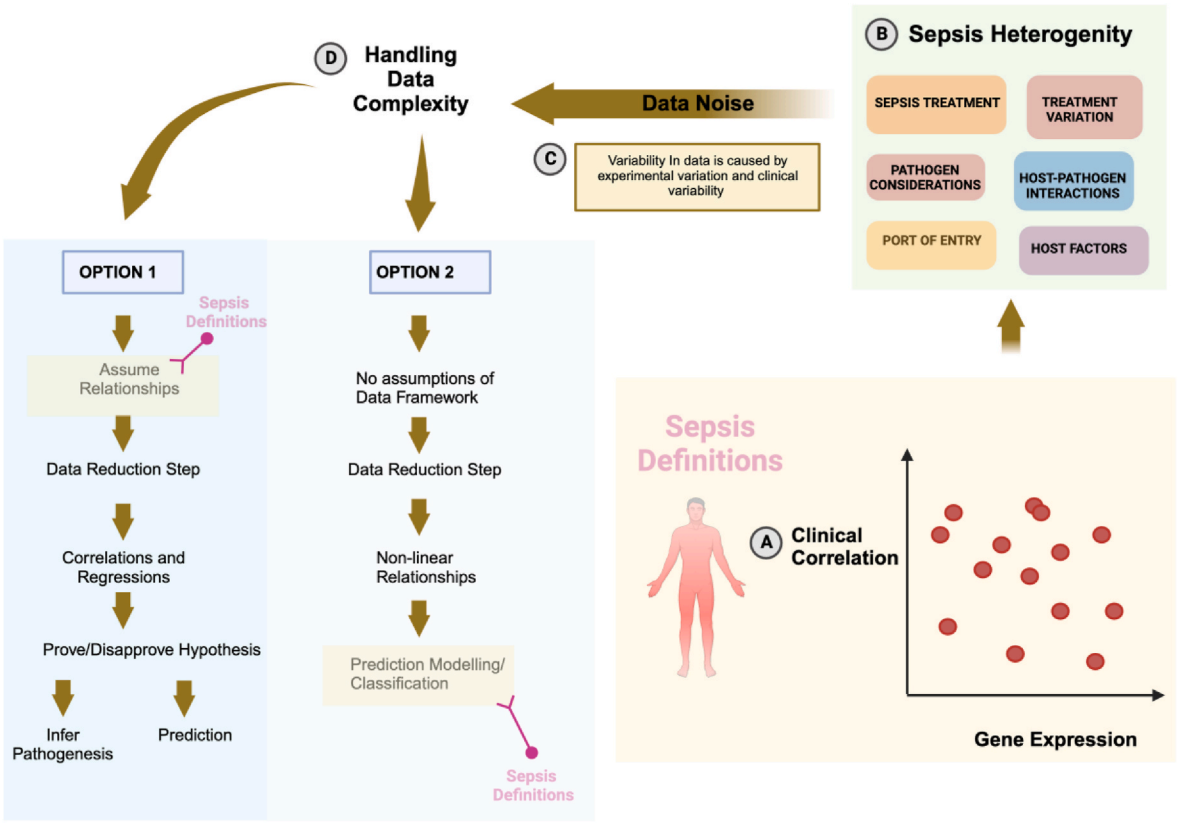

Fig. 5. Challenges in the bioinformatic interpretation in sepsis.

studies.

In charting the course for future sepsis research, it is imperative to consider adopting a bioinformatics perspective, highlighting the inherent value of a transcriptomic viewpoint. Additionally, more extensive longitudinal studies incorporating diverse blood sampling strategies are warranted. However, the challenge of early sepsis diagnosis remains prominent, especially considering that the clinical manifestations may initially be inconspicuous. To bridge the existing gap between scientific discoveries and their clinical implementation in the realm of sepsis, future research efforts should emphasize the seamless integration of cutting-edge approaches, notably transcriptomics, into clinical settings for personalized diagnostics. In addition, using artificial intelligence (AI) and machine learning techniques holds substantial promise for deciphering complex gene expression data, ultimately enhancing the accuracy of disease classification and the development of tailored treatment strategies. Given the intricate nature of sepsis and the anticipated non-linear data relationships from a gene expression standpoint, the application of machine learning to this domain exhibits significant potential. As illustrated in Fig. 6, advanced algorithms and machine-learning techniques can help decipher the complexities of gene expression data, providing a clearer and more precise understanding of disease classification and treatment strategies. These strategies can overcome the inherent complexities of sepsis research, ultimately advancing the field toward more precise and personalized care of patients with sepsis. Moreover, advancements in sepsis definition and identification of reliable biomarkers can significantly enhance benchmarking processes, extending their relevance across various clinical aspects of sepsis. Future investigations should delve deeper into understanding how transcriptomics can offer a dynamic perspective that effectively translates to bedside applications.

Crucially, gene expression methodologies, as elucidated in this study, offer immense potential for validating consensus-driven approaches for sepsis management. They provide a means to bridge the existing knowledge gaps in sepsis pathophysiology and refine clinical protocols through precision strategies. Furthermore, exploring the potential utility of gene expression biomarkers in augmenting existing tools at bedside and in laboratory settings is a promising avenue. These biomarkers have the potential to aid in prediction, thereby supporting precision management strategies for sepsis, with the ultimate goal of modifying the risk profile associated with this condition. The rapid development of technologies capable of expeditiously processing high-throughput gene expression data may enable the practical application of transcriptomics in acute sepsis scenarios. The possibility of performing transcriptomic analyses at the bedside could enhance the real-time applicability of such methods to patient care. Overall, by addressing limitations and embracing future directions, the field of sepsis can continue to evolve based on a transcriptomic approach, offering improved strategies for the diagnosis, treatment, and care of patients with sepsis.

In this study, we present a comprehensive research framework with potential clinical applicability and established essential links to critical components relevant to sepsis. However, the components of the framework were introduced based on the clinical experience of researchers. A significant challenge exists within the sepsis research field, in that there is an absence of consensus regarding appropriate terminology and definitions. The lack of such an agreement has contributed to the scarcity of studies in certain critical sepsis categories, emphasizing a central issue: the absence of a precise and universally accepted definition of sepsis. This inherent ambiguity is a limitation of the present study, stemming from the blurred boundaries between research terminologies, especially concerning clinical descriptors, such as sepsis severity and progression. Furthermore, there is a considerable gap between the wealth of scientific insights into sepsis and its practical clinical applications. This gap is exacerbated by the complexities inherent in sepsis research, including platform heterogeneity, challenges related to the timing of sample collection, and variations arising from host-pathogen interactions. These intricacies pose significant barriers to seamlessly integrating the findings from diverse sepsis studies.

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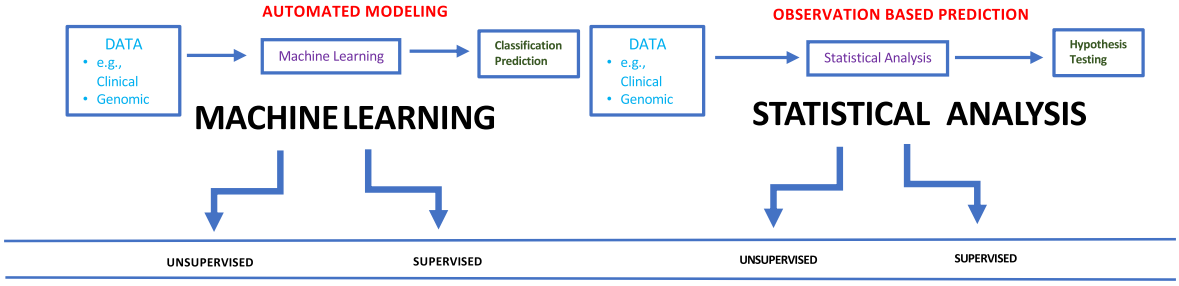

Analysis Type	Use Dimensional reduction?	Use past analysis to predict the future	Use Dependent Variables	Use Independent Variables	Data is used to model generalizability	Loss and risk descriptors	Predictors/ Features are Assumed	Models assumed to be parametric	MAIN AIM
Statistics	YES	YES	Yes	Yes	YES	Mean Squared Error	Yes	Yes	Testing of uncertainty and hypothesis
Machine Learning	YES	YES	Yes, known as Targets	Yes, Known as Features	YES	Mean Squared Error	No	NO	Classification Prediction and Forecasting

Fig. 6. Comparing the application of machine learning and statistical analysis in sepsis.

care of patients with sepsis.

5. Conclusion

This narrative review underscores the potential of a transcriptomic-oriented approach as a pivotal tool for bridging knowledge gaps between pathophysiological changes and cellular modifications applied to the clinical context. The transcriptomic-oriented framework used in this study spanned various sepsis categories: diagnosis, progress, severity, endotyping, classification, biomarking, and benchmarking. This revealed the application of transcriptomics across numerous aspects of sepsis, offering promising avenues for integration with other omics strategies and interpretive frameworks. Nonetheless, the inherent complexities and interpretive challenges of sepsis were persistently echoed throughout this review. Future research should investigate sealing the gaps between biological changes translated into a clinical context. By adopting a transcriptomic-driven methodology, researchers and clinicians can collectively navigate the intricacies of sepsis, directing future progress and facilitating improved patient outcomes from sepsis.

Fig. 1. An important direction for bioinformatics research applied to sepsis is the correlation of bench side findings to the bedside. Genomic clinical research can involve the collection of blood samples at specific milestones or time points in Sepsis **[A]**. In transcriptomic studies, gene expression can be measured to reflect the amalgamation of gene interactions and downstream pathway changes reflecting sepsis pathogenesis. This methodology leads to gene expression patterns of interest **[B]**. From the genetic material, it is possible to generate intricate data through microarray or high-throughput gene sequencing (RNA-seq or sc-RNA-seq). To achieve this, reverse transcription of mRNA to cDNA is required **[C]**. Analysis of gene expression can occur by various methods depending on the goals of the study **[D]**. Ultimately, the process as described allows for the exploration of the relationship between cellular changes (based on gene expression) and biological consequences manifested by the patient. We believe these are exciting times for clinical research to learn about mRNA and its application to sepsis. Particularly given the ability now to affect the machinery of transcription through CRISPR-Cas9 **[E]**.

Fig. 2. Using transcriptomic information to support translating clinical sepsis research to the bedside. Key questions linking gene expression (GE) to the framework are shown (central boxes). These then support components of the research framework (Diagnosis/Definition, Disease Progression, Disease Severity, Biomarking, and Benchmarking). mRNA is thus vital for cellular function and consists of mRNA protein-coding and non-protein-coding RNA functions. The two facets allow mRNA to play a role in gene code translation for protein synthesis and a gene regulatory role. Essentially, mRNA is the genetic mediator guiding ribosomal protein synthesis based on information provided in the DNA. At this moment, transcriptomics aims to document gene activity by quantifying mRNA, analyzing gene expression patterns, and measuring gene levels in sepsis.

Gene-to-gene connections are shown, with genes illustrated as nodes. The interconnections between genes represent regulatory relationships. Therefore, network interactions among genes form a Gene Regulatory Network (GRN). Sepsis is a heterogeneous process affected by host factors such as age, infection timing, and pathogen-associated factors.

Red and dark blue are clinical attributes; green pertains to a biological construct related to a cellular function or clinical endpoint; yellow depicts a standard against which other parameters are compared. In light blue are the target endpoints, which can be deduced from the data features, according to the generated (vector) data points for each patient.

1. Sepsis diagnosis and definition are interrelated. Changes in cellular activity can be detected with respect to mRNA, providing patterns indicative of a pathophysiological response indicative of sepsis. This resulted in GE patterns that were consistent with the diagnosis and definition of sepsis.
2. Sepsis progression is important because if unabated, it can progress to multi-organ dysfunction syndrome (MODS). Single-organ dysfunction in sepsis is rare, with subsequent failure of each organ being associated with an increased risk of poor outcomes [72]. The Sepsis 3 Task Force concluded that the misleading model that sepsis follows a continuum from severe sepsis to shock was misleading [17]. Furthermore, the task force concluded that the term severe sepsis was redundant.
3. The application of transcriptomic methods to sepsis has been used to predict organ dysfunction. Scoring systems help quantify the degree of organ dysfunction. Sequential Organ Failure Assessment (SOFA) score is used in adult sepsis and pediatric logistic organ dysfunction (PELOD) in children.
4. An essential aim of transcriptomic analysis is to improve the application of clinical therapies in a more precise approach, mindful of the host-pathogen complexity. The aim of this study was to tailor therapies according to a specific profile or sepsis subtype. Sepsis Subtyping may be performed from a gene function perspective, such as according to a distinct pathophysiological mechanism known as endotypes.
5. Understanding how the transcript correlated to disease severity allows the linkage of mRNA GE, a proxy of cellular function, to clinical categorization.

The clinical categories of different severity levels include sepsis, severe sepsis, and septic shock. Relating the gene transcript to different levels of disease severity could provide insights into sepsis pathogenesis and provide an interpretation of the host-infection relationship.

6. The relationship between biomarkers and gene expression is of particular interest, especially from a temporal perspective, allowing the tracking of sepsis, and therefore, understanding disease trends when managing patients. This can be used in predictive capacity and to preempt disease progression, thereby providing information to the clinician in making management choices.
7. The transcript may also have value in benchmarking sepsis, such as correlating to clinical variables, standards, and endpoints.

Transcriptomics provides the ability to enhance endpoint analysis, aiding disease categorization/classification and prognostication.

One of the challenges in developing a clinical research framework for sepsis is that the components defining the framework may not be clear because of a lack of clarity in the original definition of sepsis. Therefore the likely overlap between components, for example, thought endotype, could allow the clustering of groups of patients; this approach may also have value as part of a biomarking strategy.

Fig. 3. Studies were first selected (10th July 2023) using the Pubmed web server according to selective keywords related to the framework headings (see methods). The identified studies were then screened, excluding review articles and including gene expression studies [Keyword Search Term: '(gene expression) not (review)']. Human studies in the last ten years were then deemed eligible. Non-drug, vaccine, non-high throughput gene (HGT) studies and only research published in English were included in the final narrative analysis [Keyword Search term: not (drugs) not (vaccines) and (English)]. For the category **'Sepsis Endotype'** the search strategy was changed as the title search only eluded to three studies; instead, a search through the text identified 64 studies, of which 17 were deemed eligible (2 were letters and comments to the editor and the third was a protein study). This left 14 included as HGT studies and for narrative review (Fig. 2A). In the category **'Sepsis Biomarker'** 409 studies were identified after screening; this filtered the studies to 30, of which 23 were eligible, and six were included after exclusion (Fig. 2B). In the **'Sepsis Definition'** category 125 studies were identified of which non were eligible after

screening(Fig. 2C). For '**Sepsis Diagnosis'** 19 papers were deemed eligible, which after the exclusion, led to 15 studies of which only 7 were HGT studies (Fig. 2D). For **'Sepsis Progression,'** 124 studies were identified, 17 after screening, of which only nine were eligible, and two were included for narrative analysis (Fig. 2E). For '**Sepsis Severity**,' 19 papers were eligible; after exclusion, this eluded 2 HGT studies (Fig. 2F). For '**Sepsis Benchmark'** the search strategy was changed to extend the search strategy through the body of the document (Fig. 2G).

Fig. 4. Biomarkers **[A]** detect quantifiable alterations, while Endotypes **[B]** define traits based on molecular, cellular, genetic, or immunological characteristics. The term "Endotype," originates from "endogenous phenotype," denoting disease subtypes characterized by distinct biological mechanisms rather than solely observable symptoms. On the other hand, "Biomarkers" refers to objectively measurable entities. Biomarkers are crucial in clinical settings, enabling the monitoring of diseases such as sepsis. The practical application of Endotype markers (Endomarkers) in acute scenarios for real-time translation to the patient's bedside presents challenges. However, the interconnectedness offered by Endomarkers, linking sepsis and pathogenic mechanisms, underscores their significance in advancing precision medicine strategies.

Fig. 5. A key objective of Omic methods, like transcriptomics, is to establish connections between bedside observations and genomic-level insights. To undertake a holistic interpretation based on the large datasets generated from gene sequencing or microarray requires the ability to handle the generated data. An important goal of analysis is to discern relationships and gain bioinformatic insights from the gathered gene expression data **[A]**. Sepsis presents substantial heterogeneity, arising from various factors spanning pathogen and host considerations, host attributes (e.g. host genetics), host-pathogen interactions, and the primary site of infection **[B]**. Upon generating the gene expression data, addressing noise originating from experimental and clinical variations is a crucial step **[C]**. Two potential approaches are available for data handling **[D]**. Option 1 involves the conventional statistical approach, which necessitates assumptions about data structure, making it suitable for inference studies involving hypothesis testing and prediction. Option 2, however, is tailored for modeling without assuming a specific data framework, rendering it suitable for non-linear data analysis and predictive/classification modeling, such as provided by Machine Learning a branch of Artificial Intelligence. Crucially, the absence of a universally applicable sepsis definition poses an inherent challenge in sepsis studies, attributable to the multifactorial nature and inherent heterogeneity of the disease process.

Fig. 6 presents a comparison between the (SA) and Machine Learning (ML) approaches. Both the SA and ML methods can be categorized as supervised or unsupervised, and they share similar variable definitions, resulting in generalizable models. SA is primarily hypothesis driven, making assumptions about the available features and employing parametric models. In contrast, ML models may be non-parametric and their structures may be unknown without assuming a normal data distribution or linearity. ML is oriented toward tasks such as classification and prediction for pattern detection without a priori knowledge of the underlying structure.

Both ML and SA use the mean square error for loss and risk estimation. Dimensionality reduction is beneficial for handling large datasets for both SA and ML. In ML, dimensional reduction helps to prevent data overfitting. In SA, the generalizability of the model relies on establishing a connection between the data and the population that it represents. However, achieving generalizability in ML can be more challenging than in SA because issues such as model overfitting may arise. ML can be used to handle complex and skewed data.

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Data availability

All cited literature has been used for this scoping review and is available as per the references provided by journals in the public domain.

CRediT authorship contribution statement

Asrar Rashid: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. **Feras Al-Obeidat:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Hari Krishnan Kanthimathinathan:** Data curation, Methodology, Writing – review & editing. **Govind Benakatti:** Data curation, Formal analysis, Supervision, Writing – review & editing. **Wael Hafez:** Data curation, Formal analysis, Investigation, Resources, Software, Validation, Writing – review & editing. **Raghu Ramaiah:** Writing - review & Editing. **Joe Brierley:** Formal analysis, Methodology, Supervision, Writing – review & editing. **Benjamin Hanisch:** Data curation, Investigation, Software, Writing – review & editing. **Praveen Khilnani:** Data curation, Investigation, Validation, Writing – review & editing. **Christos Koutentis:** Data curation, Formal analysis, Validation, Writing – review & editing. **Berit S. Brusletto:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Mohammed Toufiq:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Zain Hussain:** Data curation, Methodology, Supervision, Visualization. **Harish Vyas:** Data curation, Investigation, Resources, Writing – review & editing. **Zainab A Malik:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Maike Schumacher:** Data curation, Formal analysis, Investigation, Visualization. **Rayaz A Malik:** Data curation, Formal analysis, Investigation, Resources, Visualization. **Shriprasad Deshpande:** Data curation, Formal analysis, Investigation, Visualization. **Nasir Quraishi:** Data curation, Funding acquisition, Resources, Writing – review & editing. **Raziya Kadwa:** Data curation, Formal analysis, Writing – review & editing. **Amrita Sarpal:** Data curation, Investigation, Software, Writing – review & editing. **M. Guftar Shaikh:** Data curation, Investigation, Software, Writing – review & editing. **Javed Sharief:** Data curation, Investigation, Resources, Visualization, Writing – review & editing. **Syed Ahmed Zaki:** Data curation, Methodology, Writing – review & editing. **Rajesh Phatak:** Data curation, Resources, Writing – review & editing. **Akash Deep:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Ahmed Al-Dubai:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **Amir Hussain:** Data curation, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2023.101419.

References

[1] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200–11.

[2] Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46(Suppl 1):10–67.

[3] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181–247.

[4] Gül F, Arslantaş MK, Cinel İ, Kumar A. Changing definitions of sepsis. Turk J Anaesthesiol Reanim 2017;45(3):129–38.

[5] Obonyo NG, Schlapbach LJ, Fraser JF. Sepsis: changing definitions, unchanging treatment. Frontiers in Pediatrics 2019;6.

[6] Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med 2020;21(2):e52–106.

[7] Sprung CL, Trahtemberg U. What definition should we use for sepsis and septic shock? Crit Care Med 2017;45(9):1564–7.

[8] Souza DC, Brandao MB, Piva JP. From the international pediatric sepsis conference 2005 to the sepsis-3 consensus. Rev Bras Ter Intensiva 2018;30(1):1–5.

[9] McGovern M, Giannoni E, Kuester H, Turner MA, van den Hoogen A, Bliss JM, et al. Challenges in developing a consensus definition of neonatal sepsis. Pediatr Res 2020;88(1):14–26.

[10] Martimbianco ALC, Pacheco RL, Bagattini AM, de Fatima Carreira Moreira Padovez R, Azevedo LCP, Riera R. Vitamin C-based regimens for sepsis and septic shock: systematic review and meta-analysis of randomized clinical trials. J Crit Care 2022;71:154099.

[11] Sweeney DA, Danner RL, Eichacker PQ, Natanson C. Once is not enough: clinical trials in sepsis. Intensive Care Med 2008;34(11):1955–60.

[12] Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis 2015;15(5):581–614.

[13] Berry M, Patel BV, Brett SJ. New consensus definitions for sepsis and septic shock: implications for treatment strategies and drug development? Drugs 2017;77(4):353–61.

[14] Vandewalle J, Libert C. Sepsis: a failing starvation response. Trends Endocrinol Metabol 2022;33(4):292–304.

[15] Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6(1):2–8.

[16] van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol 2017;17(7):407–20.

[17] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10.

[18] Leligdowicz A, Matthay MA. Heterogeneity in sepsis: new biological evidence with clinical applications. Crit Care 2019;23(1):80.

[19] Lorton F, Chalumeau M, Martinot A, Assathiany R, Roue JM, Bourgoin P, et al. Prevalence, characteristics, and determinants of suboptimal care in the initial management of community-onset severe bacterial infections in children. JAMA Netw Open 2022;5(6):e2216778.

[20] Hasson D, Goldstein SL, Standage SW. The application of omic technologies to research in sepsis-associated acute kidney injury. Pediatr Nephrol 2021;36(5):1075–86.

[21] Fernandez-Sarmiento J, Schlapbach LJ, Acevedo L, Santana CR, Acosta Y, Diana A, et al. Endothelial damage in sepsis: the importance of systems biology. Front Pediatr 2022;10:828968.

[22] Ruiz-Rodriguez JC, Plata-Menchaca EP, Chiscano-Camón L, Ruiz-Sanmartin A, Pérez-Carrasco M, Palmada C, et al. Precision medicine in sepsis and septic shock: from omics to clinical tools. World J Crit Care Med 2022;11(1):1–21.

[23] McLean AS, Shojaei M. Transcriptomics in the intensive care unit. Lancet Respir Med 2022;10(9):824–6.

[24] Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5(1):1–9.

[25] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467–73.

[26] Zhang Z, Pan Q, Ge H, Xing L, Hong Y, Chen P. Deep learning-based clustering robustly identified two classes of sepsis with both prognostic and predictive values. EBioMedicine 2020;62:103081.

[27] Antcliffe DB, Burnham KL, Al-Beidh F, Santhakumaran S, Brett SJ, Hinds CJ, et al. Transcriptomic signatures in sepsis and a differential response to steroids. From the VANISH randomized trial. Am J Respir Crit Care Med 2019;199(8):980–6.

[28] Yehya N, Thomas NJ, Wong HR. Evidence of endotypes in pediatric acute hypoxemic respiratory failure caused by sepsis. Pediatr Crit Care Med 2019;20(2):110–2.

[29] Baghela A, Pena OM, Lee AH, Baquir B, Falsafi R, An A, et al. Predicting sepsis severity at first clinical presentation: the role of endotypes and mechanistic signatures. EBioMedicine 2022;75:103776.

[30] Goh C, Burnham KL, Ansari MA, de Cesare M, Golubchik T, Hutton P, et al. Epstein-Barr virus reactivation in sepsis due to community-acquired pneumonia is associated with increased morbidity and an immunosuppressed host transcriptomic endotype. Sci Rep 2020;10(1):9838.

[31] Kwok AJ, Allcock A, Ferreira RC, Cano-Gamez E, Smee M, Burnham KL, et al. Neutrophils and emergency granulopoiesis drive immune suppression and an extreme response endotype during sepsis. Nat Immunol 2023;24(5):767–79.

[32] Darden DB, Dong X, Brusko MA, Kelly L, Fenner B, Rincon JC, et al. A novel single cell RNA-seq analysis of non-myeloid circulating cells in late sepsis. Front Immunol 2021;12:696536.

[33] Sweeney TE, Liesenfeld O, Wacker J, He YD, Rawling D, Remmel M, et al. Validation of inflammopathic, adaptive, and coagulopathic sepsis endotypes in coronavirus disease 2019. Crit Care Med 2021;49(2):e170–8.

[34] Banerjee S, Mohammed A, Wong HR, Palaniyar N, Kamaleswaran R. Machine learning identifies complicated sepsis course and subsequent mortality based on 20 genes in peripheral blood immune cells at 24 H post-ICU admission. Front Immunol 2021;12:592303.

[35] Scicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL, et al. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. Lancet Respir Med 2017;5(10):816–26.

[36] Wong HR, Salisbury S, Xiao Q, Cvijanovich NZ, Hall M, Allen GL, et al. The pediatric sepsis biomarker risk model. Crit Care 2012;16(5):R174.

[37] Lu J, Chen R, Ou Y, Jiang Q, Wang L, Liu G, et al. Characterization of immune-related genes andimmune infiltration features for early diagnosis, prognosis and recognition of immunosuppression in sepsis. Int Immunopharm 2022;107:108650.

[38] Baghela A, An A, Zhang P, Acton E, Gauthier J, Brunet-Ratnasingham E, et al. Predicting severity in COVID-19 disease using sepsis blood gene expression signatures. Sci Rep 2023;13(1):1247.

[39] Baghela AS, Tam J, Blimkie TM, Dhillon BK, Hancock REW. Facilitating systems-level analyses of all-cause and Covid-mediated sepsis through SeptiSearch, a manually-curated compendium of dysregulated gene sets. Front Immunol 2023;14:1135859.

[40] Zheng X, Luo Y, Li Q, Feng J, Zhao C, Lu J, et al. Two gene set variation index as biomarker of bacterial and fungal sepsis. BioMed Res Int 2020;2020:8182358.

[41] Zhang JX, Xu WH, Xing XH, Chen LL, Zhao QJ, Wang Y. ARG1 as a promising biomarker for sepsis diagnosis and prognosis: evidence from WGCNA and PPI network. Hereditas 2022;159(1):27.

[42] Huang J, Sun Z, Yan W, Zhu Y, Lin Y, Chen J, et al. Identification of microRNA as sepsis biomarker based on miRNAs regulatory network analysis. BioMed Res Int 2014;2014:594350.

[43] Li J, Zhou M, Feng JQ, Hong SM, Yang SY, Zhi LX, et al. Bulk RNA sequencing with integrated single-cell RNA sequencing identifies BCL2A1 as a potential diagnostic and prognostic biomarker for sepsis. Front Public Health 2022;10:937303.

[44] de Almeida RJ, de Lima Hirata AH, de Jesus Rocha LA, de Arruda Motta MD, Varela P, Martins L, et al. Similar hypothyroid and sepsis circulating mRNA expression could be useful as a biomarker in onthyroidal illness syndrome: a pilot study. Arch Endocrinol Metab 2023;67(5):e000625.

[45] Bauer M, Giamarellos-Bourboulis EJ, Kortgen A, Möller E, Felsmann K, Cavaillon JM, et al. A transcriptomic biomarker to quantify systemic inflammation in sepsis - a prospective multicenter phase II diagnostic study. EBioMedicine 2016;6:114–25.

[46] Schaack D, Siegler BH, Tamulyte S, Weigand MA, Uhle F. The immunosuppressive face of sepsis early on intensive care unit-A large-scale microarray meta-analysis. PLoS One 2018;13(6):e0198555.

[47] Reyes M, Filbin MR, Bhattacharyya RP, Billman K, Eisenhaure T, Hung DT, et al. An immune-cell signature of bacterial sepsis. Nat Med 2020;26(3):333–40.

[48] Wynn JL, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, et al. The influence of developmental age on the early transcriptomic response of children with septic shock. Mol Med 2011;17(11–12):1146–56.

[49] Karakike E, Giamarellos-Bourboulis EJ, Kyprianou M, Fleischmann-Struzek C, Pletz MW, Netea MG, et al. Coronavirus disease 2019 as cause of viral sepsis: a systematic review and meta-analysis. Crit Care Med 2021;49(12):2042–57.

[50] Aschenbrenner AC, Mouktaroudi M, Kramer B, Oestreich M, Antonakos N, Nuesch-Germano M, et al. Disease severity-specific neutrophil signatures in blood transcriptomes stratify COVID-19 patients. Genome Med 2021;13(1):7.

[51] Sohn KM, Lee SG, Kim HJ, Cheon S, Jeong H, Lee J, et al. COVID-19 patients upregulate toll-like receptor 4-mediated inflammatory signaling that mimics bacterial sepsis. J Kor Med Sci 2020;35(38):e343.

[52] Barh D, Tiwari S, Weener ME, Azevedo V, Goes-Neto A, Gromiha MM, et al. Multi-omics-based identification of SARS-CoV-2 infection biology and candidate drugs against COVID-19. Comput Biol Med 2020;126:104051.

[53] Kalantar KL, Neyton L, Abdelghany M, Mick E, Jauregui A, Caldera S, et al. Integrated host-microbe plasma metagenomics for sepsis diagnosis in a prospective cohort of critically ill adults. Nat Microbiol 2022;7(11):1805–16.

[54] Lukaszewski RA, Jones HE, Gersuk VH, Russell P, Simpson A, Brealey D, et al. Presymptomatic diagnosis of postoperative infection and sepsis using gene expression signatures. Intensive Care Med 2022;48(9):1133–43.

[55] Xu X, Bu B, Tian H, Wu R, Yang J. MicroRNAs combined with the TLR4/TDAG8 mRNAs and proinflammatory cytokines are biomarkers for the rapid diagnosis of sepsis. Mol Med Rep 2022;26(5).

[56] Zhou X, Wang Y, Chen J, Pan J. Constructing a 10-core genes panel for diagnosis of pediatric sepsis. J Clin Lab Anal 2021;35(3):e23680.

[57] Sweeney TE, Wynn JL, Cernada M, Serna E, Wong HR, Baker HV, et al. Validation of the sepsis MetaScore for diagnosis of neonatal sepsis. J Pediatric Infect Dis Soc 2018;7(2):129–35.
[58] Fiorino C, Liu Y, Henao R, Ko ER, Burke TW, Ginsburg GS, et al. Host gene expression to predict sepsis progression. Crit Care Med 2022;50(12):1748–56.
[59] Glibetic N, Shvetsov YB, Aan FJ, Peplowska K, Hernandez BY, Matter ML. Transcriptome profiling of colorectal tumors from patients with sepsis reveals an ethnic basis for viral infection risk and sepsis progression. Sci Rep 2022;12(1):20646.
[60] de Jong TV, Guryev V, Moshkin YM. Estimates of gene ensemble noise highlight critical pathways and predict disease severity in H1N1, COVID-19 and mortality in sepsis patients. Sci Rep 2021;11(1):10793.
[61] Weber LM, Saelens W, Cannoodt R, Soneson C, Hapfelmeier A, Gardner PP, et al. Essential guidelines for computational method benchmarking. Genome Biol 2019;20(1):125.
[62] Altman MC, Rinchai D, Baldwin N, Toufiq M, Whalen E, Garand M, et al. Development of a fixed module repertoire for the analysis and interpretation of blood transcriptome data. Nat Commun 2021;12(1):4385.
[63] Sweeney TE, Khatri P. Benchmarking sepsis gene expression diagnostics using public data. Crit Care Med 2017;45(1):1–10.
[64] Scicluna BP, Uhel F, van Vught LA, Wiewel MA, Hoogendijk AJ, Baessman I, et al. The leukocyte non-coding RNA landscape in critically ill patients with sepsis. Elife 2020;9:e58597.
[65] Yee CR, Narain NR, Akmaev VR, Vemulapalli V. A data-driven approach to predicting septic shock in the intensive care unit. Biomed Inf Insights 2019;11:1178222619885147.
[66] Shappell C, Rhee C, Klompas M. Update on sepsis epidemiology in the era of COVID-19. Semin Respir Crit Care Med 2023;44(1):173–84.
[67] Goodacre S, Fuller GW. New guidance on initial antimicrobial treatment of sepsis. BMJ 2022;377:o1354.
[68] Stang AS, Straus SE, Crotts J, Johnson DW, Guttmann A. Quality indicators for high acuity pediatric conditions. Pediatrics 2013;132(4):752–62.
[69] Robb MA, McInnes PM, Califf RM. Biomarkers and surrogate endpoints: developing common terminology and definitions. JAMA 2016;315(11):1107–8.
[70] Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol 2011;127(2):355–60.
[71] Kataria Y, Remick D. Sepsis biomarkers. In: Walker WE, editor. Sepsis: methods and protocols. New York, NY: Springer US; 2021. p. 177–89.
[72] Lelubre C, Vincent J-L. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol 2018;14(7):417–27.