Review

Strength of Omics in Uncovering Sepsis Mechanisms-A Perspective

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ABSTRACT: Background: Sepsis is a significant life-threatening condition due to a dysregulated response to infection. Large datasets yield unprecedented views and transformative insights into processes through various computational frameworks. Our aim was to highlight significant contributions from genomics, transcriptomics, proteomics in the field of sepsis, as modeled from human data. We are showcasing key findings in each omics that have improved the understanding of sepsis pathophysiology, while presenting a perspective from the group's own contribution to the field. Discussion and Conclusions: Each of the presented omics has advanced our mechanistic understanding on sepsis pathogenicity, biomarker identification for diagnosis, prognosis, and molecular stratification purposes. Multi-omics sepsis research shows strong input from genomics, transcriptomics, proteomics. These have revealed mechanistic links and produce robust endotypes but faces challenges on the path to clinical integration. Integrative sepsis studies combine large-scale omics, paired sampling, and computational multi-omics frameworks to link molecular layers to phenotype. Addressing gaps in standardization, and age/ethnicity representation could yield actionable biomarkers, stratified therapies and improved outcomes.

KEYWORDS: *Omics, sepsis, genomics, transcriptomics, proteomics, metagenomics.*

Introduction

Sepsis is a significant life-threatening condition due to a dysregulated response to infection.

Global data place sepsis as responsible for 1 in 5 deaths, with reported incidence estimates with large regional variation, at least in part dependent on country welfare [1-3].

Accurately assessing the true burden of the disease is challenging.

Incidence reports vary between the use of various data sources-clinical data, health claims data, or electronic health records [4].

Definitions can also vary largely-diagnosis of sepsis is still largely stratified according to the Sepsis-2 criteria-systemic inflammatory response syndrome (SIRS) criteria [5]-to the most recent Sepsis-3 criteria using Sequential Organ Failure Assessment (SOFA) [6]; incidence of sepsis may even higher using Sepsis-3 criteria [7].

Last but not least, comprehensive data is missing, especially so in low-and middle-income countries [4].

Epidemiological data on sepsis in Romania only relies on single-center reports [8-11] , with contributions from our group [12].

Sepsis is a heterogeneous condition, influenced by factors such as age, comorbidities, infectious agent [13].

Pathophysiologically, there is a dysregulated immune response, with both hyper-inflammatory and immunosuppressive phases, potentially leading to organ dysfunction Despite considerable effort, molecular, cellular and tissular mechanisms in sepsis are still incompletely understood [14-18].

There is a need for specific biomarkers and a better understanding of the adaptive or maladaptive nature of sepsis mechanisms to improve diagnostic precision and to tailor therapeutic approaches by sepsis endotype [15].

To tackle this complex issue, multi-omics analyses have contributed greatly, with the use of bioinformatic and machine learning tools [19].

Understandably so, omics are transforming our grasp on the mechanisms in sepsis, with the discovery of involved biological pathways, the

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enhancement of our understanding of cellular functions and disease processes, and the facilitation of a holistic systems biology approach.

Objective

Our aim was to highlight significant contributions from genomics, transcriptomics, proteomics, in the field of sepsis, as modeled from human data.

Given the involvement in pathogenicity, a more recently developed omics, metagenomics are also brought into attention.

We have not set out to comprehensively review technologies developed for interrogation, integration, interpretation, and insights of each omics, but rather to showcase the contribution, caveats and latent potential for these omics.

Given our group's involvement in the field as part of the Functional Genomics Group Romania accessible at https://hfgpr.com/; Human Functional Genomics Project https://humanfunctionalgenomics.org/, we have seen firsthand how large datasets yield unprecedented views and transformative insights into processes through various computational frameworks.

In this context, we are also discussing work from our group, as part of the FUSE (Functional Genomics in Severe Sepsis) project, accessible at https://emediqual.umfcv.ro/ro/fuse.

Lastly, we are speculating on further research avenues to take to uncover the underpinnings of sepsis at a molecular level and prepare for translational work.

Methods

To review the current literature on omics approaches in sepsis research, a comprehensive analysis of studies involving human subjects was conducted.

Relevant articles published in English were retrieved from multiple databases, including Google Scholar, PubMed, ScienceDirect, Springer Link, and Scopus.

The search strategy utilized a combination of key terms such as "sepsis", "severe infection", "genomics", "transcriptomics", "metagenomics", "biomarker discovery", immune response", and "cytokine production".

We selected studies exploring the alterations associated with sepsis, as well as the potential of various omics in uncovering mechanisms useful for early diagnosis, prognosis, and treatment response.

This review aimed to address the following research questions: "What insights do omics studies provide into the underlying mechanisms of sepsis and potential therapeutic targets?"; "What are the advantages and limitations of omics studies in sepsis research?"; "How else can current approaches be used to further knowledge?".

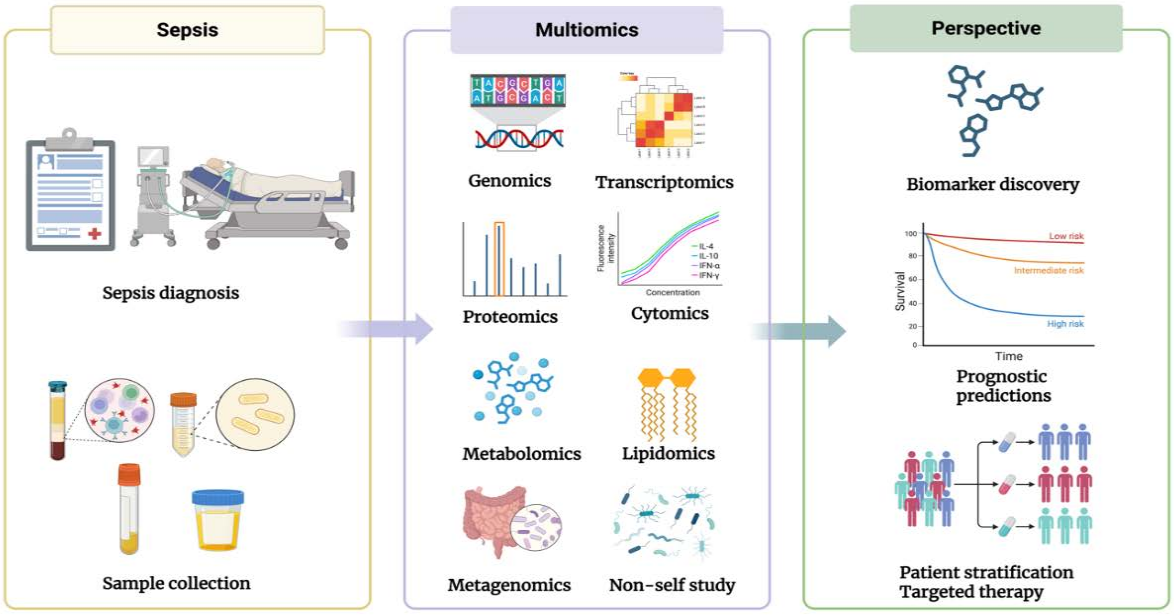

Figure 1. Overview of the multi-omics approach in tackling sepsis. Created in https://BioRender.com. Link to the figure-https://app.biorender.com/illustrations/68dfd3e97ec9be9c864d1d35

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Omics-one relevant contribution at a time

By synthesizing data from diverse approaches, this article offers a narrative overview of the role of different omics in sepsis research, one omics at a time, towards improving the understanding of sepsis pathophysiology, while presenting a perspective from the group's own contribution to the field (Figure 1).

Genomics

Should we explore genetic factors in sepsis? Epidemiological data is supportive of its genetic predisposition: death from infection was markedly increased in biological full siblings [20]; there is familial clustering in sepsis-significantly more cases of sepsis occurred among first-and second-degree relatives [21]; large scale genealogical and registry analyses bring compelling proof [22].

Rare pathogenic variants in genes are associated with primary immunodeficiencies in children with sepsis [23,24].

These examples of inborn errors of immunity linked to sepsis are a minority of cases. Other rare variants have been proven to play a less prominent role, with scarce examples. The burden of rare variants in the *ABCC8* and *TRPM4* genes have been associated with a protective effect of central nervous system dysfunction in pediatric sepsis [25].

Rare variants were found in the complement system among patients with infectious purpura fulminans, a severe form of sepsis with coagulopathy [26].

Common variation in genes involved in innate immunity, cytokine production, and coagulation have been linked to sepsis outcomes; tumor necrosis factor α and interleukin-1 receptor antagonist, *TNF-α*, *IL-6*, and *IL-8* genes have been associated with sepsis [27].

Genome-wide association studies approaches have provided further hints that genetic predisposition plays a role in sepsis susceptibility, severity and outcome-each conditioned by different genetic determinants. In a population-specific GWAS study, susceptibility to sepsis has been associated with locus 8p23.1, which harbors defensins, [28].

Susceptibility to postoperative sepsis and surgical site infections has been associated with variants on chromosomes 9 and 14 [29].

Polymorphisms (SNPs) associated with mortality in septic shock patients showed that non-coding variation in a cluster near *CISH* gene involved in cytokine signaling is linked to septic shock [30].

Survival in pneumonia sepsis identified *FER* as a protective gene. The *SAMD9* gene, involved in the inflammatory response, was linked to decreased 28-day survival in sepsis patients [31].

Advances in GWAS studies are noticeable, as is its functional validation studies. Regulatory and mechanistic variants identified by GWAS were moved from association to causal inference using functional assays to show how variants alter host immune regulation [28].

Survival-model GWAS design tailored to sepsis endpoints have advance of the field [31].

A mechanistic route to mortality-*VPS13D* rs6685273 was linked to altered IL-6 cytokine production by integrating functional cellular GWAS with clinical association [32].

Genetic variants that alter cytokine expression after infection (cytokine QTLs) help explain inter-individual differences in sepsis.

Large-scale genomic and functional-genomic studies have mapped eQTLs, modQTLs, and regulatory networks that explain heterogeneity in sepsis (unpublished data in our group as part of the ImHoGen, a multi-ancestry consortium encompassing twelve independent cohorts partnered with HGFP) [33,34].

Most common variants found show small effect sizes [35].

It may well be that common variants of large effect may not significantly influence sepsis susceptibility or mortality Small effect size variation can be used for the development of polygenic risk scores (PRS) as a population genomics tool towards precision approaches:

PRS for traits such as hematocrit, granulocyte count, and C-reactive protein levels have been linked to septic shock susceptibility and mortality [36];

PRS for Sepsis-2 and Sepsis-3 show both separate and shared genetic variation [35] among the two. Ancestry-matched PRS and clinical variables substantially improve 28-day mortality prediction compared with clinical models alone, highlighting the need for population specificity in sepsis genomics [37].

Yet, the clinical application of these identified biomarkers remains limited [38].

PRS usefulness awaits broader multi-ethnic validation, mechanistic linkage, and prospective demonstration of impact.

Nonetheless, mechanistic understanding of the intricate genomic landscape is essential, as is translating genetic insights into effective prevention and treatment strategies.

Transcriptomics

Transcriptomic analysis has contributed to a paradigm shift in sepsis from a simple biphasic inflammatory model to a view of heterogeneous, dynamic host responses.

Mapping RNA transcripts to canonical signaling pathways has revealed distinct patterns in sepsis. Notably, genes linked to pro-inflammatory, anti-inflammatory, and mitochondrial dysfunction pathways exhibit increased expression, whereas those associated with translation initiation, mTOR signaling, adaptive immune responses (particularly T cell function), and antigen presentation are downregulated [39].

Interestingly, more than 80% of the bulk transcriptomic response in circulating immune cells sepsis appears to be independent of the infection's source or causative pathogen, suggesting a common molecular signature underlying sepsis pathophysiology [40,41].

This is in line to the findings in our community sepsis cohort [42], but may not be more nuanced in terms of both and organ-specific transcriptional programs across different tissues [43,44].

Multiple studies have used host transcriptome analysis to generate multi-gene biomarkers and molecular endotypes that stratify patients by biology [45,46] and outcome [47].

For instance, the SeptiCyte LAB molecular classifier, recently approved by the FDA, aids in differentiating sepsis from noninfectious systemic inflammation in critically ill patients upon ICU admission [46].

Our group has proposed a robust framework based on transcriptomics to discriminate sepsis patients and identify risk groups based on two transcriptional states: one reflecting the immune response to pathogens (resistance, R) and the another associated with systemic inflammation (SI) [48].

Notably, these gene sets have various gene contents and reach various performance [49,50], but could mean comprehensive transcriptome profiling may potentially be a tool for the clinical setting.

Transcriptomic data have proven instrumental in sub-phenotyping septic patients into molecularly distinct endotypes. These include Sepsis Response Signature (SRS) groups [51], the MARS endotypes [52], and the inflammopathic-adaptive-coagulopathic clusters [41,53].

Each subset features characteristic immune trajectories, ranging from robust inflammatory states to marked immunosuppression, that show divergent clinical courses. This endotypic classification is thus key to understanding why certain patients deteriorate rapidly, whereas others recover despite apparently similar infections or clinical presentations.

Unlike the genome, the transcriptome is dynamic, changing throughout the course of sepsis and various organs. Early-versus-late dynamics and temporal cohorts show phased transcriptomic responses: an early surge of inflammatory and innate transcripts, with later persistence or decline depending on patient trajectory, while non-survivors often display delayed or muted adaptive responses and sustained inflammatory/apoptotic signatures [54].

Transcriptomics has unraveled a model where endothelial/coagulation activation, immune-driven protease, and metabolic shifts within specific organs cooperate to produce organ dysfunction [44,55,56].

Temporal transcriptomics variability has been leveraged to predict early responses to hemodynamic therapy in septic shock [57].

Moreover, evidence that sepsis subgroups respond differently to interventions (for example, corticosteroids) underscores the necessity for a precision medicine model [58].

Large-scale clinical trials are now crucial to confirm the therapeutic potential in sepsis [59].

Single-cell transcriptomics has emerged as a powerful next step, providing a granular view of how individual immune cell subsets in septic patients change over time [60].

By pinpointing rare or transiently activated populations-such as dysfunctional lymphocyte subtypes or hyper-activated monocytes-this technique elucidates mechanistic nuances that bulk transcriptomic approaches might obscure.

It further refines the characterization of sepsis endotypes and strengthens our capacity to tailor immunomodulatory therapies precisely to the cellular perturbations of each patient.

Taken together these technical advances enable robust cross-site signatures, cell-level mechanistic insights and clinically translatable assays that are driving sepsis precision medicine.

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Proteomics

Proteomics represents the extensive study of the protein set within a biological system, through methods investigating their structure and function, extending to post-translational modifications (phosphorylation, glycosylation, ubiquitination etc.) [61,62].

Proteome-centered studies in sepsis are based on samples originating from various tissues, such as the lung, liver and the kidneys, in an effort to capture organ-specific changes, extensively reviewed [63].

However, plasma, due to its more feasible collection method, represents one of most promising sample types in the identification of prognostic biomarkers, and more immediate application in clinical practice.

Proteomics continues to offer pathophysiology insights revealing a system-level molecular remodeling: at immune, coagulation, endothelial [64] and metabolic [65] axes, and their correlates.

In one study, functional enrichment analyses showed the significance of proteins involved in: complement activation, lipoprotein metabolism, regulation of inflammation and proteolysis, innate immune response [66].

The research of the past decade has pointed towards several plasma proteins acting at multiple levels in the sepsis pathophysiological axis, such as lipid metabolism, inflammatory responses and coagulation patterns [67,68]; the resulting implications for disease progression and mortality were shown to be of either protective, or deleterious nature [63,69].

Proteomics has produced candidate proteins and compact panels useful for diagnosis [70,71], prognosis [72,73], and molecular stratification [70] in sepsis endotypes.

Lipoproteins were remarkably correlated with both favorable and detrimental outcomes: APOC3 had potential anti-inflammatory effects, while APOB correlated with a higher score for organ dysfunction. Proteins responsible for complement activation indicated that the imbalance within the complement system may significantly influence disease evolution [66].

Sepsis risk and elevated levels of TCN-1 (Transcobalamin-1) and LEP (leptin), while less researched proteins, such as HIPK3 and ApoA-I, reduced 28-day mortality, an important measure of severity in sepsis; all of the proteins mentioned were suggested as potential actionable targets.

Furthermore, proteomics has also shaped a few stratification approaches for sepsis patients, and in correlation with leukocyte transcriptomic data, showed the delineation of three proteomic profiles with distinct disease evolution trajectories [74,65].

It is uncertain if these leads are truly reproducible across platforms and cohorts.

In our work, based on the potential circulating biomarkers we identified, we could stratify the sepsis cohort into inflammatory endotypes, which we defined as either “high-”, or “low-inflammatory”. We could find clinical correlates of the high inflammatory endotype: patients were significantly older, had cardiovascular comorbidities, correlated with renal and liver function, as well as lymphopenia; serum ferritin and pro-inflammatory cytokine levels. The findings of the FUSE study are also explored in a clinical trial for personalized immunotherapy in sepsis (ImmunoSep-NCT04990232) [75,76].

Proteomics is perhaps most frequently seen in integrative sepsis studies combine large-scale proteomics with bulk and single-cell transcriptomics, paired sampling, and computational multi-omics frameworks to link molecular layers to phenotype [77,78].

On this path, using a dual transcriptomic and proteomic approach, our group has confirmed a "high-inflammatory" endotype and further characterized it showing robust activation of the interferon-gamma-CXCL9-CXCL10 axis, a promising target for endotype-guided risk and therapy [42].

In the context of sepsis, proteomics may offer a better understanding of the phenotypic variation of patients, shaped by disease severity and the degree of organ dysfunction [79,74], producing reproducible biomarker panels for diagnosis and prognosis, nominating druggable pathways, and enabling patient stratification and multi-omics integration towards novel therapeutic avenues [74,65].

Metagenomics

Sepsis is widely reported to be associated with reduced microbiome diversity, loss of commensal taxa, and the expansion of potential pathogens. Microbiome alterations are an effect of sepsis and subsequent treatments but also have putative roles in sepsis onset and pathogenesis.

Microbiome profiling and the identification of dominant taxa in sepsis are now possible through various technologies-including amplicon and metagenomic sequencing, as well

as qPCR-each offering different trade-offs in cost, speed, and comprehensiveness [80-82].

The mechanisms through which the microbiome contributes to sepsis onset remain inconclusive [83].

One putative mechanism is that the reduction in SCFA-producing microbes increases gut permeability [84,85], thereby allowing pathogens to enter the system.

Notably, if gut integrity is compromised, decreased microbiome diversity is associated with sepsis onset.

For example, a study of 800 adults by [86] found that pre-transplant microbiome alpha diversity predicted critical illness after hematopoietic cell transplantation. The extent to which this is a common mechanism and whether specific microbiome alterations are implicated in sepsis onset still need to be established.

On the other hand, once sepsis is established and treatment has begun, significant changes occur, with reported losses of beneficial taxa and increases in pathogens.

An increased relative abundance of the *Enterococcaceae*, *Enterobacteriaceae*, and *Moraxellaceae* families and a decrease in the beneficial families *Lachnospiraceae* and *Bifidobacteriaceae* were reported in [87], a study on 38 sepsis cases and 19 controls, and [88], a study on 20 sepsis cases and 20 controls.

Importantly, septic patients exhibit heterogeneous intestinal microbiota patterns with no consistently dominant bacteria.

In [89], the 25 sepsis cases showed a predominance of *Proteobacteria*, *Bacteroidetes*, or *Verrucomicrobia*, whereas healthy individuals consistently displayed a stable dominance of *Firmicutes* (*Bacillota*) and *Bacteroidetes*.

The microbiome dysbiosis may affect at its turn the sepsis outcome, potentially through effects on the immune system.

In 24 patients undergoing hematopoietic cell therapy, the cases receiving fecal microbiome transplants had increased white cell counts [90], and in a 500 healthy patients cohort, effects on cytokines were detected [91].

Our group is also exploring the role of the gut microbiome in the onset and pathogenesis of sepsis (unpublished work), having as a reference a comprehensive characterization of the microbiome in healthy cohorts [92].

This and other similar datasets constitute an ethic-specific valuable resources useful for innovative therapeutic strategies such as selective decontamination, probiotics, prebiotics, synbiotics, postbiotics and fecal microbiota transplantation (FMT) [93].

For instance, positive outcomes from FMT have been reported in both mouse models [94] and human patients [95,96].

Given the variability in how individual gut microbiomes respond to sepsis, and in which microbial species become dominant, further research is needed to understand how FMT interaction with existing microbiota affects outcome. This could contribute to pave the way for more effective, personalized treatment strategies.

Underexplored areas in omics

Sepsis is not a single disease, but a syndrome with diverse etiologies and manifestations.

Sepsis research is strong in the above-described omics. Nonetheless, addressing gaps in integration, standardization, and age/ ethnicity representation could yield actionable biomarkers and stratified therapies that are translatable to the clinic.

The integration of multi-omics data sources represents a common target of sepsis research, and beyond. It faces though computational and study design barriers that call for call for integrated analyses and standardized pipelines.

Existing research is heterogenous in study design: the use of an unified case definition [74] and innovative phenotypic screens [97], diverse sepsis types based on the organ of interest, tissue and sampling time, sample size limitations and computational tools still maturing for this pathology. And last, but not least, most studies capture cross-sectionally this dynamic process-time-series multi-omics are rarely obtained, yet essential to capture evolving host responses.

Snapshots of the clinical evolution of sepsis cannot take into account the possible switch between sepsis phenotypes over the course of the disease [74,98-101].

All these causes of variability may also be accountable for the lack of feasibility in the one-size-fits-all approach that has been so far explored and prove to be significant challenges for translating such techniques, at the moment, into clinical practice [102,103].

There is a clear need to address age-specific underpowered cohorts, limited ethnic diversity, and resource-setting representation unevenness.

Strong age-dependent signatures have been documented. Pediatric and neonatal sepsis have distinct host responses [104,105], as do adults and elderly [106].

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Survival-associated proteins differ by racial background [107].

The setting may also be significant. In our study we have shown the prevalence of Gram-negative bacteria and the high incidence of *Clostridium difficile*, contrary to other reported findings in Europe [12].

Interactions between the host and the pathogen at the omics level are not fully understood. This includes how pathogens manipulate host cellular processes and how the host's immune system responds [108-110].

Additionally, host-pathogen interactions also likely to be influenced by coexisting infections [110].

Local microbiome of immunosuppressed patients can be correlated with a modified immune response to sepsis [111] and species-specific responses have been shown. These only reinforce the limitative character of universal biomarkers, or prognostic subgroups, in the absence of robust interventions targeting host-pathogen interactions [112].

Translating omics findings into clinical practice remains a challenge. There is limited translation of genetic predictive scores and sparse integration with other omics layers; stronger genomic signals could enable risk stratification and identification of host-directed targets [113].

As consensus on molecular signatures, based on proteomics or transcriptomics, to identify sepsis or its endotypes is lacking [42,76,104], there is a need for improved robust omics-based diagnostic signatures and endotype-guided therapies.

Practical considerations, such as cost and accessibility, need further exploration and are no easy feat themselves on the path to translation towards the clinical setting.

Conclusions

Multi-omics sepsis research shows strong activity in genomics, transcriptomics, proteomics, and metabolomics.

They can reveal mechanistic links and produce robust endotypes but faces challenges on the path to clinical integration.

Addressing gaps in standardization, and age/ ethnicity representation could yield actionable biomarkers and stratified therapies.

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Author Contributions

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

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Consent Statement

Not applicable.

Data availability

All data presented in the manuscript are available from the authors upon request.

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