Risk Stratification and Prognosis in Sepsis
What Have We Learned from Microarrays?

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KEYWORDS

• Sepsis • Prognostics • Gene expression • Microarray • Biomarker

KEY POINTS

- Whole-genome expression studies are a useful tool in making sense of the complex and heterogeneous changes that occur in sepsis.
- Prognosis of sepsis at admission is becoming more feasible, with recent validation of some stratification markers such as the pediatric sepsis biomarker risk model (PERSEVERE).
- Splitting patients into subgroups (endotypes) based on gene expression markers may be a way to identify more homogeneous populations of patients with sepsis.
- Better biomarkers may provide for prognostic and phenotypic enrichment strategies in future therapeutic trials.
- Both time and illness severity must be controlled for in future studies of sepsis.

INTRODUCTION

Sepsis kills more than 750,000 people in the United States annually.[1] Mortality rates have decreased in recent years as a result of clinical process improvements such as adherence to resuscitation protocols and timely administration of antibiotics[2] but remain unacceptably high. Risk stratification and prognostication in sepsis is of particular importance because high-risk patients may benefit from earlier clinical interventions, whereas low-risk patients may benefit from not undergoing unnecessary procedures. Prognostication in sepsis is currently done mostly via clinical criteria (eg, organ dysfunction and/or presence of shock) and blood lactate levels. Although useful, these approaches may not adequately reflect the diversity of clinical presentations seen. In addition, the lack of biomarkers to adequately quantify the heterogeneity of patients with sepsis may have contributed to the numerous failed drug trials in sepsis.[3] Better risk stratification could lead to successful clinical trials through predictive enrichment and prognostic enrichment.[4] Eventually, such biomarkers could personalize treatment based on where a patient resides on the spectrum of inflammation or whether specific organs are failing.

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There are multiple approaches to discovering and developing biomarkers. One such approach leverages the high throughput capabilities of transcriptomics in which thousands of genes can be simultaneously measured. These data-driven, systematic studies are particularly amenable to highly complex syndromes such as sepsis because so many changes are occurring at once. Sepsis induces profound changes in the peripheral blood transcriptome, with 70% to 80% of all genes undergoing significant changes in expression.[5,6] To understand and make sense of these changes thus requires a comprehensive view of the transcriptome. As a result, dozens of whole-genome expression studies in clinical human sepsis have now been completed. These studies mostly belong in 3 broad, often overlapping, categories: (1) studies of sepsis at onset; (2) longitudinal studies of sepsis, and (3) studies of organ-specific outcomes in sepsis.

The complexity of changes at the molecular level has made interpreting individual studies difficult for the casual reader; therefore, the authors have summarized the literature. These areas were not reviewed: (1) animal studies of sepsis, (2) studies of critical illness (ie, traumatic injuries) without sepsis, (3) studies that only sampled later time-points in sepsis (more than 48 hours after onset), (4) studies of acute infection only without sepsis, and (5) studies of sepsis that only examined small numbers of genes (ie, studies not using highly parallel technologies). The focus was on synthesizing both validated clinical findings and recurring themes across studies of whole blood or sorted leukocytes evaluating gene expression in sepsis.

PROGNOSTICATION OF MORTALITY AT ADMISSION: GENE EXPRESSION AT THE ONSET OF SEPSIS

The first microarray study in clinical sepsis was published in 2004; the principle findings were that two-thirds of all genes assayed were differentially expressed, and that septic inflammation was distinctly different from the inflammation that underlies other critical illness.[7] Since that time, both findings have been confirmed my much larger studies with more advanced technologies.[5,6,8,9] Having found that septic inflammation can be distinguished from nonseptic inflammation, the next question was whether subtypes of sepsis both known (ie, survivors and nonsurvivors) and unknown (ie, new classifications based on gene expression patterns) could be discovered in gene expression data. Pachot and colleagues[10] established that, within a cohort, gene expression patterns in early sepsis could divide survivors from nonsurvivors; however, these results were likely over fit (a common failing in high-dimensional data) because the gene expression pattern that distinguished survivors from nonsurvivors has not been independently validated.

Several other studies have also examined how gene expression in early sepsis differs between eventual survivors and nonsurvivors. Reproduced findings in nonsurvivors include an early decrease in adaptive immunity compared with innate immunity,[11–13] disrupted cell cycle control genes,[12,14,15] increases in protease and metal-ion regulation pathways,[12,14] and increased expression of innate inflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-18 (**Table 1**).[11,12,16] On the other hand, two studies reported either no or very few genes significantly differently regulated between eventual survivors and nonsurvivors at sepsis onset.[5,17]

Another way to stratify patients in a supervised fashion is to examine illness severity instead of the binary outcome of mortality. Although such studies might not be immediately clinically actionable (because a gene expression model to predict a clinical score is made redundant by that clinical score), they might provide pathophysiologic insights or potential markers for risk stratification. Results have been mixed. One group reported that subjects with worse outcomes show a greater degree of change in their gene expression profiles,[18] whereas another reported that among subjects with septic shock more genes were differentially regulated in the lower-severity group than in the higher-severity group (as measured by the simplified acute physiology score).[19] A more targeted approach is to study correlation coefficients between severity scores and gene expression.[20] Almansa and colleagues[12] found modest but significant correlation (mostly absolute Spearman rho<0.5) between the expression levels of 55 genes and sequential organ failure assessment scores (SOFAs) of subjects with sepsis; however, no model of severity was constructed. Such widely divergent results in the study of sepsis severity and mortality are likely explained both by differences in underlying biology between different cohorts and strong confounding from technical and informatics approaches, sampling time, and study design.

More important than qualitative differences in the transcriptome of survivors is a testable clinical model. Here the hypothesis is that a set of genes with a trained predictive model could give a probability of mortality at the time of admission. The pediatric sepsis biomarker risk model (PERSEVERE) is probably the best-validated