Profiling of blood transcriptome to unravel causal pathways in pediatric septic shock

Leland Dunwoodie, MD[1]; Mihir Atreya, MD, MPH[2]; Andrew J. Lautz, MD[2]
[1]Department of Pediatrics and [2]Division of Critical Care Medicine, Cincinnati Children's Hospital Medicine Center

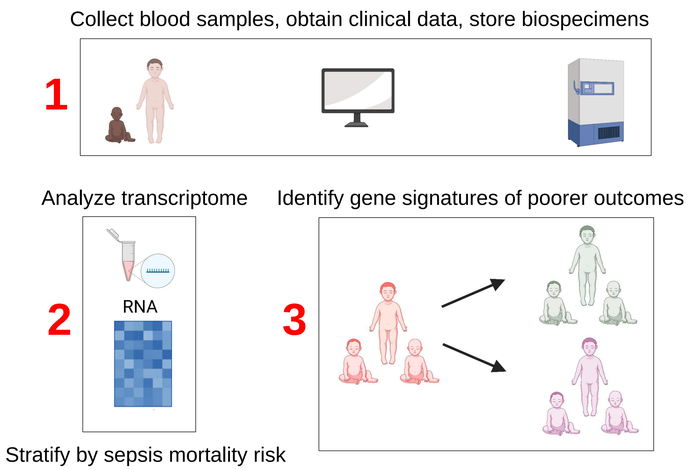
Background

In the U.S. alone, 7,000 lives are lost to pediatric sepsis annually. The Pediatric Sepsis Biomarker Risk Model (PERSEVERE)-II has been prospectively validated to identify children at high risk for mortality from sepsis. However, biological features distinguishing children with sepsis at high risk for mortality from those at low risk remain unknown. A comprehensive assessment of this biology may inform development of targeted therapeutic interventions among at-risk patients. As such, **our objective is to identify differences in the blood transcriptome of children at high- and low-risk for mortality with septic shock,** leading to novel prognostic and therapeutic targets.

Methods

1. Obtain blood samples from 81 children with septic shock on day 1 of PICU admission.
2. Assign PERSEVERE-II mortality risk; there were 23 high-risk and 58 low-risk samples.
3. Quantify gene expression of each sample with whole-transcriptome analysis of 20,030 genes.
4. Identify differentially-expressed genes comparing children with low- and high-mortality risk.

Graphical Summary



Differential Gene Expression

Differentially-expressed genes were identified using DESeq2. At an adjusted p-value of 0.001, **we found 517 genes overexpression and 278 genes repressed among high-risk pediatric patients with septic shock.**

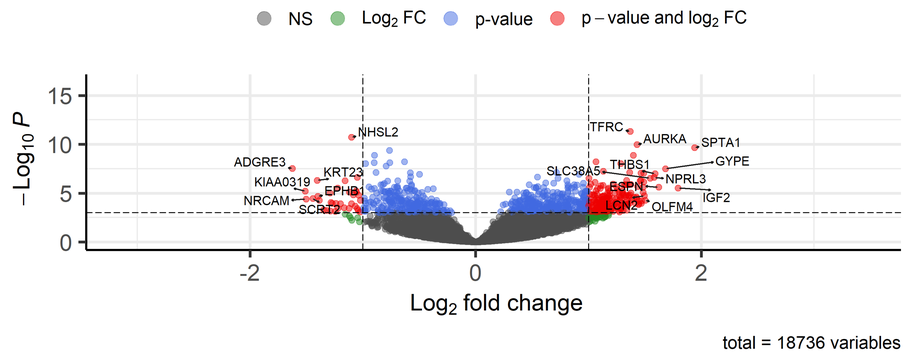


Figure 1. Differentially expressed genes overexpressed (right side of figure) or repressed (left side of figure) comparing transcriptomic profiles of children with high- and low-mortality risk based on PERSEVERE-II biomarkers. Highlighted genes in red have a Benjamini-Hochberg adjusted p-value of < 0.001 and a |log2FoldChange| > 1.

Cell Type Deconvolution

We further analyzed our transcriptome data with CIBERSORTx, which imputes cell type proportions from gene expression data. **We found a significantly lower proportion of mature neutrophils in high-risk patients** (35%) compared to high-risk patients (46%): p = 0.006 using two-tailed t-test.

Conclusion

We identified many genes differentially-regulated in children with septic shock. **Children at high risk for mortality are characterized by their innate immune response, as evidence by activation of cell cycle genes and a lower proportion of mature neutrophils.** This uncontrolled host response likely contributes to mortality.

Functional Annotation of Differentially-Expressed Genes

The functions of differentially-expressed genes were explored using clusterProfiler. **Genes overexpressed in high-risk patients are involved in cell turnover, while genes repressed in high-risk patients are involved in the adaptive immune system.**

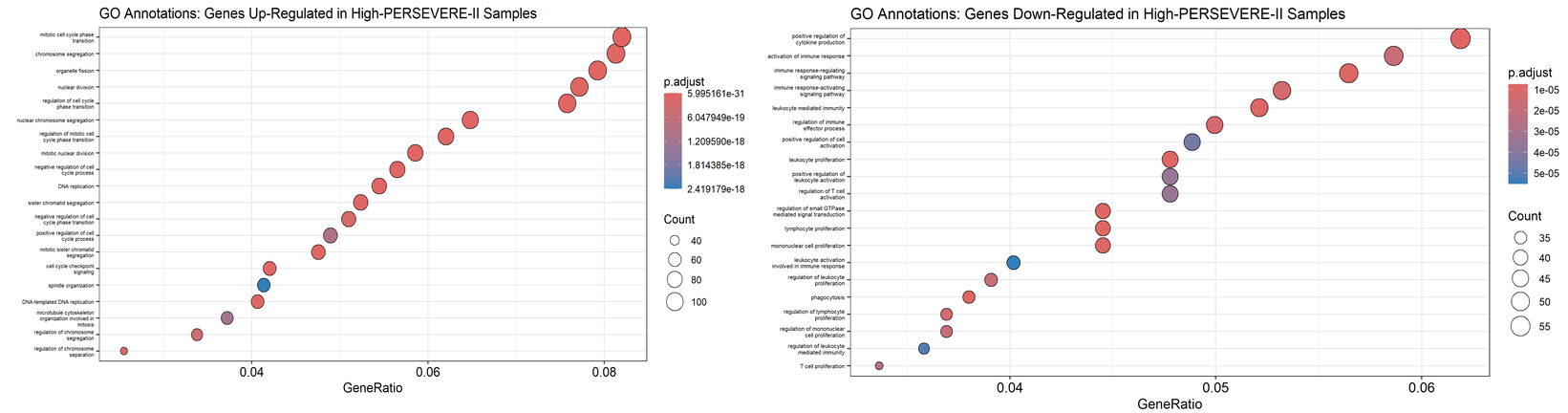


Figure 2. Gene Ontology annotations enriched among genes overexpressed (left panel) or repressed (right panel) in high-risk children with sepsis to suggest the function of identified differentially expressed genes.