ICU
MANAGEMENT & PRACTICE

Molecular Phenotypes to Advance Precision Care in ARDS

The heterogeneity of acute respiratory distress syndrome (ARDS) has played a role in hindering successful pharmacotherapy in clinical trials. To address this, researchers have identified two molecular phenotypes of ARDS - hypoinflammatory and hyperinflammatory - through latent class analysis (LCA) applied to protein biomarkers and clinical data across various cohorts. These phenotypes have been consistent across multiple trials and observational studies.

The hyperinflammatory phenotype, characterised by elevated proinflammatory biomarkers and decreased protein C and bicarbonate, has shown higher mortality rates in previous ARDS trials. These phenotypes respond differently to interventions such as positive end-expiratory pressure, fluid management, and simvastatin. However, several questions remain unanswered, including their identification in earlier recruitment trials, response to neuromuscular blockade, and the key biological pathways differentiating the phenotypes.

The Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial focused on early neuromuscular blockade in moderate to severe ARDS to address these questions. Leveraging data from ROSE, researchers applied latent class analysis to identify phenotypes using baseline clinical data and protein biomarkers. They also analysed whole-blood transcriptomes in a subset of patients to deepen understanding of the biological features of each phenotype, including dynamic changes over time and post-transcriptional protein correlates of differentially expressed genes. Despite early recruitment and enriched severity, no treatment benefits were observed with cisatracurium therapy in the ROSE trial.

The trial investigated the efficacy of cisatracurium in moderate to severe ARDS. Researchers aimed to address three key questions regarding the identified molecular phenotypes: 1) Whether the same phenotypes appear in a more severe ARDS cohort with earlier recruitment; 2) Whether these phenotypes exhibit differential responses to neuromuscular blockade; and 3) Which biological pathways are most significant in differentiating between the inflammatory phenotypes.

Latent class analysis was conducted using pre-enrollment clinical data and protein biomarkers. Additionally, whole-blood RNA sequencing was performed in a subset of patients (n = 134) using samples collected at enrollment and on Day 2. Differential gene expression and pathway analyses were then conducted based on the sequencing data. Subsequently, further plasma proteins were measured, and their abundance was assessed relative to the amounts of gene expression identified in the analysis.

The hypoinflammatory (60.4%) and hyperinflammatory (39.6%) phenotypes were identified, exhibiting similar biological and clinical characteristics to previous studies. The hyperinflammatory phenotype showed higher mortality at Day 90 than the hypoinflammatory phenotype (30.3% vs. 61.6%). No treatment interaction was observed between the phenotypes and randomised groups concerning mortality. The hyperinflammatory phenotype was enriched for genes associated with innate immune response, tissue remodelling, and zinc metabolism at Day 0 and collagen synthesis and neutrophil degranulation at Day 2. Changes in gene expression patterns over time varied depending on survivorship. While most highly expressed genes correlated with the abundance of their corresponding plasma proteins, no correlation was observed for the class-defining plasma proteins identified in the latent class analysis with their corresponding genes' expression.

These findings show that the hyperinflammatory and hypoinflammatory phenotypes in ARDS exhibit distinct clinical, protein, and dynamic transcriptional characteristics. These differences underscore the potential of molecular phenotypes to advance precision care in ARDS, both clinically and biologically.

Source: AJRCCM
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