

Identification of Septic Shock Subgroups for Fluid Strategy Formulation: A Multi-Omics Integrated Approach

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Commentary

Septic shock is characterized by systemic inflammation, vasodilation, and organ hypoperfusion, often necessitating aggressive fluid resuscitation to restore intravascular volume and improve tissue perfusion [1]. However, the administration of intravenous fluids is a double-edged sword. While it can improve hemodynamics, excessive fluid administration can lead to complications such as fluid overload, pulmonary edema, and dilutional coagulopathy [2,3]. Current guidelines lack precision in recommending fluid strategies, leading to variability in clinical practice. Some clinicians advocate for early and liberal fluid administration, while others prefer a more restrictive approach with early vasopressor use [4]. This variability underscores the need for a more personalized approach to fluid management in septic shock.

The management of septic shock remains one of the most challenging aspects of critical care medicine, with fluid resuscitation being a cornerstone of therapy. Despite its widespread use, the optimal fluid strategy—whether liberal or restrictive—remains a subject of intense debate [5]. The study by Zhang *et al.* published in *Nature Communications* represents a significant step forward in addressing this issue by employing a multi-omics approach to identify subgroups of septic shock patients who may benefit from tailored fluid strategies [6].

Zhang *et al.* [6] leveraged a multi-omics approach, integrating transcriptomics and proteomics, to identify subgroups of septic shock patients with differential responses to fluid strategies. The study included 494 septic shock patients, divided into training and validation cohorts, and used RNA sequencing to quantify gene expression across thousands

of transcripts. The authors developed a "benefit score" based on transcriptomic data, which predicted the likelihood of a patient benefiting from a restrictive fluid strategy. This score was then validated in an independent cohort, demonstrating its potential clinical utility.

The study identified 13 genes that interacted with treatment effects, providing insights into the molecular mechanisms underlying the differential responses to fluid strategies. Notably, patients who adhered to the recommended fluid strategy based on their benefit score had significantly improved survival outcomes. The authors further developed a proteomic signature comprising six proteins, which showed moderate performance in predicting which patients would benefit from a restrictive fluid strategy. This proteomic signature, while requiring further validation, represents a promising step toward the development of rapid, clinically applicable biomarkers for guiding fluid management in septic shock.

The findings of this study have several important implications for clinical practice. First, they highlight the heterogeneity of septic shock and the need for personalized treatment strategies. By identifying subgroups of patients who are more likely to benefit from restrictive or liberal fluid strategies, clinicians can tailor their approach to individual patients, potentially improving outcomes and reducing complications associated with inappropriate fluid administration [2,3]. Second, the study underscores the potential of multi-omics approaches in critical care medicine. While transcriptomic data provided valuable insights, the development of a proteomic signature offers a more practical tool for clinical application, given the stability and direct biological relevance of proteins.

However, the current assays for these proteins require further optimization to meet the rapid decision-making needs of the intensive care unit (ICU).

The article discusses the differential gene expression patterns observed among patients reacting differently to restrictive fluid strategies, with involved genes participating in significant biological processes such as cell activation, membrane potential regulation, platelet activation, complement cascade, and cell-cell adhesion [7-10]. In the context of sepsis, immune cells' activation leads to the release of inflammatory mediators that disrupt endothelial function, enhancing vascular permeability by damaging tight junctions and the glycocalyx layer. In this article, the differential expression analysis revealed significant differences between the restrictive and liberal fluid strategy groups, highlighting CSF3, MICB_MICA, and CXCL9. For example, CSF3, crucial for granulocyte production and function, is linked to benefits from a liberal fluid strategy in managing conditions like chemotherapy-induced neutropenia and septic shock. Thus, higher CSF3 values indicate increased benefits from a liberal fluid strategy.

Despite its significant contributions, the study has several limitations. The categorization of fluid strategies into liberal and restrictive groups, while necessary for analysis, may oversimplify the complex decision-making process in clinical practice. Additionally, the study did not account for the specific types of fluids used (e.g., balanced vs. unbalanced solutions), which could influence outcomes [11,12]. Future studies should explore the impact of different fluid types on patient outcomes, particularly in the context of the identified subgroups. Moreover, the generalizability of the findings may be limited by the study's population, which was predominantly from Chinese hospitals. Validation in more diverse populations is essential to ensure the applicability of the benefit score and proteomic signature across different ethnic and geographic groups.

In conclusion, the study by Zhang *et al.* represents a significant advancement in the field of septic shock management. By integrating multi-omics data, the authors have identified subgroups of patients who may benefit from tailored fluid strategies, paving the way for more personalized and precise treatment approaches. The development of a proteomic signature, while still in its early stages, holds promise for guiding clinical decision-making in real-time. As the field of critical care medicine continues to embrace precision medicine, studies like this will be instrumental in improving patient outcomes and reducing the morbidity and mortality associated with septic shock.

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Authors' Contribution

The commentary was conceptualized, written, and approved by the author.

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