Journal of Translational Medicine

LETTER TO THE EDITOR Open Access

Critical evaluation of "Multi-omics analysis reveals distinct spatial compartmentalization of lung repair niches in pediatric ARDS"

Zubaida Bibi[1*] and Kausar Ali[2]

Dear Editor,

We read with keen interest the recent study by Song et al. examining spatial and single-cell transcriptomic patterns of injury and repair in pediatric acute respiratory distress syndrome (PARDS) [1]. The authors should be commended for their innovative integration of spatial transcriptomics, scRNA-seq, BALF profiling, and plasma proteomics to address a critical gap in pediatric lung biology. While the findings are compelling and hypothesis generating, several important limitations warrant consideration when interpreting the conclusions.

First, a comparison between a single juvenile lung that survived and one that died is the basis for the central spatial and tissue-level studies. PARDS is a biologically heterogeneous syndrome impacted by age, immune maturity, ventilatory exposure, and comorbidities. Previous research on ARDS biomarkers highlights that results from very small samples could not be generalizable and are susceptible to patient specific effects rather than outcome defining processes [2].

Second, the comparison of lung specimens is subject to marked temporal confounding. The lung from the deceased patient reflects end stage disease, whereas the survivor lung represents a later phase of recovery following prolonged mechanical ventilation and extracorporeal membrane oxygenation. Consequently, the observed molecular and spatial differences attributed to survival may instead reflect distinct time points along the injury repair continuum rather than divergent biological pathways. Given that biomarker expression evolves substantially over time, as demonstrated in longitudinal PARDS studies, cross-sectional comparisons are inherently limited and preclude robust causal inferences [3, 4].

Third, although plasma keratin-17 (KRT17) is proposed as a prognostic biomarker, the study does not conclusively determine its lung specific tissue origin. Previous systematic reviews of ARDS biomarkers highlight that circulating markers often reflect systemic inflammation or epithelial injury from multiple sources rather than alveolar specific repair processes, limiting their specificity for lung pathology [5].

Finally, methodological constraints inherent in these technologies limit the interpretation of spatial and single-cell transcriptomic data, especially when applied to a very limited number of specimens. The accuracy of spatial deconvolution is highly dependent on reference datasets and may not fully capture unusual or transitional cell states. Such limitations require careful interpretation, particularly in research lacking biological replication, according to current methodological assessments [6].

In conclusion, this significant study offers insightful information about possible geographic healing niches in PARDS, although it should be considered hypothesis-generating rather than definitive. Confirmation of the suggested pathways and biomarker utility will require validation in larger, longitudinal, multi-center pediatric populations.

*Correspondence:
Zubaida Bibi
drzubaida241@gmail.com
[1]Ayub Medical College Abbotabad, Abbotabad, Pakistan
[2]KUST Kohat, Kohat, Pakistan

Funding
No funding was received for this work.

Data availability
No new data was created and generated in this work.

Declarations

Ethical approval
Not applicable.

Informed consent
Not applicable.

Conflict of interest
Authors declares no conflict of interest.

Received: 30 December 2025 / Accepted: 15 January 2026
Published online: 10 April 2026

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