Intensive Care Med
https://doi.org/10.1007/s00134-025-08230-3

CORRESPONDENCE

Diagnosing delirium: the emerging role of biomarkers

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We enjoyed the article by Kotfis et al. calling for precise terminology describing global cognitive dysfunction, particularly as it relates to in-hospital delirium as a phenotypic manifestation of acute encephalopathy [1]. The authors identified how this inconsistent use of terminology creates challenges for healthcare delivery and research advancement [1]. The authors called on the research community to focus efforts on two priorities: (1) objective assessment tools to facilitate the diagnosis of distinct phenotypes of acute encephalopathy and (2) research to elucidate causal pathways in the development of delirium [1]. We concur with the authors' perspective and propose focusing on clinical biomarker identification.

Biomarkers are reliable diagnostic tools that can objectively diagnose disease and predict prognosis [2]. The identification of biomarkers to diagnose delirium could supplement or replace current subjective screening tests, particularly in cases where depressed patient alertness precludes assessment. Novel biomarkers may also point towards potential pathophysiological pathways, guiding new research and advancing our understanding of the mechanisms of delirium and its subsequent phenotypic manifestations [2].

We identified novel biomarkers associated with postoperative delirium within the Vascular Events in Surgery Patients Cohort Evaluation Cardiac Surgery Biobank [3]. We examined a sample of 30 patients with delirium diagnosed on postoperative day one matched to 30 controls by age, sex, ethnicity, center, and cardiopulmonary bypass time [3]. We performed a comparative proteomic analysis using samples obtained on postoperative day three [3]. Figure 1 shows the protein expression patterns of the top three differentially expressed biomarkers. We undertook pathway enrichment analyses and found that these biomarkers for delirium (FKBP1B, C2CD2L, RAB6B) are proteins that are highly expressed in neurons and regulate calcium and molecular transport. The identification of these previously unidentified proteins supports their promise as diagnostic tools and highlights unidentified pathophysiological mechanisms in the development of postoperative delirium [3].

Based on these promising results, we are expanding our work in an international multi-center prospective cohort study to evaluate the predictive and diagnostic relationships of these biomarkers with the incidence of delirium in patients undergoing cardiac surgery. We hope this work will confirm the results of our exploratory analysis and lead to the use of these biomarkers as diagnostic screening tools, provide insight into the pathobiological mechanism of postoperative delirium development and, in doing so, unify the unsubstantiated dichotomy in the literature between delirium and acute encephalopathy, as identified by Kotfis et al.

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This comment refers to the article available online at https://doi.org/10.1007/s00134-025-08124-4.

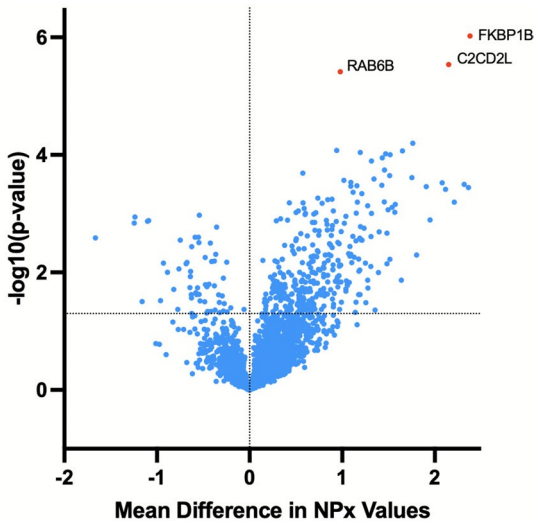

Fig. 1 Volcano plot illustrating the association of 2,856 blood proteins with delirium status. The x-axis shows the average difference in normalized protein expression (NPx) values (log2-based protein expression levels) between cases and controls; positive values to the right of the vertical dotted line indicate proteins whose levels are higher in delirium cases relative to controls, and negative values on the x-axis indicate biomarkers whose levels are lower in cases. The y-axis displays statistical significance represented as − log10 transformed P values. Higher values on the y-axis indicate associations that are more statistically significant (lower P values). The horizontal dotted line delineates the statistical significance threshold for nominal significance. The top three biomarkers associated with delirium are highlighted

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Data availability statement
Data may be made available on request made to the corresponding author (J.S.).

Declarations

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Human and animal studies
All human and animal studies have been approved by the Hamilton Integrated Research Ethics Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Publisher's Note

Received: 10 November 2025 Accepted: 18 November 2025
Published online: 24 November 2025

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