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Subject: Letter to the Editor on "Diagnostic and prognostic performance of urine ubiquitin carboxy-terminal hydrolase L1 across multiple acute brain injury types – A longitudinal prospective cohort study"

Dear Editor,

I am writing to express my thoughts on the recently published study by Hellström et al. (2025) on the diagnostic and prognostic value of urine ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) in acute brain injury (ABI) patients. This study presents an intriguing avenue for non-invasive biomarker research in ABI and warrants further discussion on certain key aspects.

The authors demonstrate that urine UCH-L1 levels were significantly elevated in ABI patients compared to healthy controls, suggesting its diagnostic potential. However, the inability of urine UCH-L1 levels to differentiate between favorable and unfavorable outcomes raises questions regarding its prognostic utility. The authors attribute this to possible dilution effects in urine, which is a valid concern given the variability of urinary biomarkers.

One notable strength of the study is its prospective longitudinal design, which allowed the authors to evaluate temporal changes in UCH-L1 levels. The observation that UCH- L1 levels remained elevated for up to 10 days post-injury is valuable and suggests that urine-based diagnostics may be feasible even beyond the acute phase. However, the study would have benefited from a larger sample size to enhance statistical power, particularly in distinguishing between different types of ABI.

An additional consideration is the normalization of UCH-L1 levels to creatinine. The authors note that normalization did not improve discriminatory performance, which is in line with previous findings (Kohlhase et al., 2023). This highlights the need for standardization in urinary biomarker research, particularly in ABI, where factors such as renal function and hydration status could impact biomarker concentration.

Despite these limitations, the findings of Hellström et al. (2025) provide a foundation for future research. Given the non-invasive nature of urine sampling, further studies should explore the integration of UCH-L1 with other established biomarkers, such as glial fibrillary acidic protein (GFAP) and neurofilament light (NfL), to improve diagnostic accuracy. Additionally, assessing urine UCH-L1 in a broader cohort, including mild traumatic brain injury cases, could provide further insights into its clinical applicability.

In conclusion, while the study effectively underscores the diagnostic utility of urine UCH-L1, its prognostic limitations warrant further investigation. Future research should aim to refine its clinical application by addressing issues related to normalization, sample variability, and potential multi-biomarker approaches.

Thank you for the opportunity to comment on this important study. I look forward to further advancements in this field.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: no conflict If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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