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Letter to the Editor

Serum GFAP and UCH-L1 are not Suitable as Diagnostic Biomarkers for Mild Traumatic Brain Injury

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Letter to the Editor

We read with interest the article by Kopcinovic *et al*. on a prospective, multicenter observational study investigating the suitability of serum glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) as biomarkers for diagnosing mild traumatic brain injury (mTBI) within 12 hours of emergency department admission [1]. In the 822 patients included, the combination of both biomarkers (mTBI assay) showed high sensitivity for diagnosing mTBI [1]. The results of the mTBI assay were age-dependent [1]. The study is interesting, but some points require further discussion.

Firstly, patients with suspected but not confirmed mTBI were included in the study [1]. To assess the validity of the mTBI assay as a diagnostic biomarker for mTBI, it is crucial to include only patients with confirmed mTBI. Including patients with suspected mild traumatic brain injury (mTBI) has the disadvantage of potentially including patients without mTBI, which could skew the results and render the conclusions unreliable. Therefore, it is recommended to repeat the analysis exclusively with patients with confirmed mTBI.

Second, it was not reported how many patients had elevated levels of both parameters prior to the trauma [1]. Since GFAP can be elevated due to dementia, multiple sclerosis, neuromyelitis optica spectrum disorder, Parkinson's disease, hereditary ataxia, GFAP astrocytopathy, neurosyphilis, encephalitis, brain tumor, hepatic encephalopathy, and epilepsy [2], it is crucial to exclude patients with pre-existing central nervous system (CNS) disorders of this type, as the biomarkers under investigation may have already been elevated prior to mTBI. These disorders were not mentioned in the exclusion criteria [1].

Third, the study was conducted partly during the pandemic (February 2022 to June 2024), but it was not reported how many of the enrolled patients were SARS-CoV-2 positive and how many were SARS-CoV-2 negative [1]. Knowledge of the proportion of included SARS-CoV-2-positive patients is crucial, as SARS-CoV-2 infections can manifest with a variety of abnormalities in the CNS, which may also be associated with an increase in GFAP or UCH-L1 [3].

The fourth point is that cerebral computed tomography (CCT), but not cerebral magnetic resonance imaging (cMRI), was used to assess a morphological cerebral lesion [1]. CCT is known to be inferior to cMRI in documenting morphological lesions in patients with traumatic brain injury (TBI) [4]. Therefore, it is likely that in some patients where no lesion was detected on CCT, a lesion would be detectable on cMRI.

The fifth point is that serum GFAP concentrations are highly dependent on the function of the blood-brain barrier (BBB) [5]. To be detectable in serum, GFAP must cross the BBB after its production in astrocytes [5]. Therefore, any conditions that alter BBB permeability can affect serum GFAP levels. GFAP is even recommended as a biomarker for BBB integrity [5]. Factors influencing BBB function include age, blood pressure, infections, medications, metalloproteinases, microRNAs, and more.

Until all factors affecting serum levels of GFAP and UCH-L1 have been elucidated and until the criteria and technologies for diagnosing mTBI are improved, these two parameters cannot be recommended as biomarkers for mTBI.

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