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Commentary

Searching for a traumatic brain injury biomarker to aid clinical decision making in the emergency department

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The need for objective prognostic biomarkers to help in the clinical management of head injury is huge: missed diagnoses and different injuries and susceptibilities limit efforts to predict consequences, advise victims, and offer useful prognosis. Most traumatic brain injury (TBI) is represented by concussion or mild TBI, for which there are no simple, objective, reliable tests [1]. The long-term consequence of chronic traumatic encephalopathy (CTE) [2] is not currently predictable except from awareness that repetitive trauma from contact sports increases risk [3]. CTE is just the tip of the iceberg: mild TBI affects an estimated 42 million individuals annually [4]. We need objective biomarkers to help patient management across the entire spectrum of head injury, from mild to major, acute to chronic.

Triage in the Emergency Departments (ED) for TBI is and will remain, for the foreseeable future, a clinical decision. The primary issue is whether a significant structural brain lesion requires inpatient observation or possible neurosurgical intervention and intensive care. Along with clinical assessment, computerised tomography (CT) is the principal additional predictor for management choices [5]; absence of any structural abnormality such as hemorrhage or brain shift usually results in a short visit or discharge. Of many approaches to find additional prognostic indicators, blood is a widely investigated source, with components added from damaged brain. An increase in several proteins after mild TBI has been replicated across multiple research groups [1], especially for S100B, that is incorporated in Scandinavian practice [6].

In this discovery stage of TBI research, a major challenge is whether candidate biomarkers are helpful in clinically relevant situations. In this article of *EBioMedicine*, Endre Czeiter and colleagues take an important step in the early effort to test candidates in "the real world" [7]. They report the relative performance potential to guide the clinical care path from 6 serum biomarkers collected within 24 h of head injury in the large multi-center Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) Core Study. The work is carried out and described well for such a huge study, reporting assays of 6 biomarkers from 2867 patients, in 65 clinical sites, in 18 countries.

To achieve meaningful comparison, uniform clinical decision rules and National Institutes of Health Common Disease Elements protocols [8] were used and, while CT conformed to local guidelines, all images were read and blood assays performed in an unbiased manner in central locations. Data support the overall conclusion that one protein, glial fibrillary acidic protein, GFAP, may supplement clinical decision-making in the ED: it predicted CT need better than clinical assessment alone. The results are promising because they were achieved with research assays rather than clinically robust, point-of-care tests. There was no added gain from the other 5 biomarkers, including S100B. Other advantages emphasise the value and sensitivity of GFAP as a biomarker: it predicted CT data across the full range of mild to severe TBI. It was the best of all 6 biomarkers in correlating with 44 of the subsets of 152 individuals who had subsequent brain structural lesions detected by MRI after initial normal CT imaging.

This study will hopefully encourage development of a refined GFAP assay to improve accuracy. Armed with such a method, ED clinicians will learn how GFAP could help their care decisions by testing over shorter timeframes, more often after TBI, and by investigating how gender and ethnic/racial differences influence GFAP levels. In addition to suboptimal assay rigor (a feature of new assays, not investigator incompetence), limitations in this study arise from the overall limited understanding of functional measures of TBI. Are there more informative biomarkers? How does GFAP add to other technologies, including quantitative EEG [9] or eye tracking [10]? Importantly, more blood candidates can be evaluated by legacy research of the stored samples.

This project demonstrates that a large multi-centre real world study can be done even without optimisation of each single part. A well-conceived and coordinated strategy, multi-national funding, transparency between many cultures, and the best of clinical work enabled this research. These results indicate the need for companies to improve quality control for precision and widespread distribution/use of a GFAP assay. The world is becoming aware of the need for reproducible, widely distributed, and economical assays for Covid-19; this study indicates we need a good GFAP assay as surrogate marker for the challenges of clinical TBI care.

Declaration of Competing Interest

Dr. Harrington has nothing to disclose.

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Author's contribution

MGH is responsible for literature search, data analysis and interpretation, and writing the manuscript.

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