Advances in Traumatic Brain Injury Biomarkers

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Abstract

Traumatic brain injury (TBI) is increasingly a major cause of disability across the globe. The current methods of diagnosis are inadequate at classifying patients and prognosis. TBI is a diagnostic and therapeutic challenge. There is no Food and Drug Administration (FDA)-approved treatment for TBI yet. It took about 16 years of preclinical research to develop accurate and objective diagnostic measures for TBI. Two brain-specific protein biomarkers, namely, ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein, have been extensively characterized. Recently, the two biomarkers were approved by the FDA as the first blood-based biomarker, Brain Trauma Indicator™ (BTI™), via the Breakthrough Devices Program. This scoping review presents (i) TBI diagnosis challenges, (ii) the process behind the FDA approval of biomarkers, and (iii) known unknowns in TBI biomarker biology. The current lag in TBI incidence and hospitalization can be reduced if digital biomarkers such as hard fall detection are standardized and used as a mechanism to alert paramedics to an unresponsive trauma patient.

Introduction And Background

Overview of neurotrauma and traumatic brain injury diagnosis

Traumatic brain injury (TBI) is a burgeoning public health problem worldwide [1,2]. The US Department of Defense formally defined TBI as a "traumatically induced structural injury or physiological disruption of brain function as a result of an external force" [3], and interagency initiatives help widespread acceptance of the definition [4]. Upon a neurological examination, the following alterations would be evident: (i) any period of loss of or decreased consciousness; (ii) loss of memory for events immediately before or after injury (amnesia); (iii) focal neurological deficits such as muscle weakness, loss of vision, and change in speech; and (iv) alteration in mental state such as disorientation, slowed thinking, and confusion [4]. Within the United States, TBI accounts for over 300,000 hospital admissions and 2.2 million emergency department visits each year [5-7]. TBI is a form of acquired brain injury and is best diagnosed at the time of injury or within the first 24 hours. It may be open (penetrating) or closed (non-penetrating). The Glasgow Coma Scale (GCS) uses impairment of consciousness, a clinical hallmark of acute brain injury, as a diagnostic measure [8]. The GCS has provided a practical method for bedside assessment to categorize patients as mild, moderate, and severe [9]. Although less than 10% of TBI cases are severe, they account for more than 80% of the total related global cost which is estimated to be 400 billion dollars/year [10,11]. The management of severe TBI (featuring compromised cranial vault/space-occupying lesions, medically refractory intracranial hypertension) starts with surgical debridement, and despite its effectiveness in increasing survival, there is no clear correlation with improving outcomes [12,13]. TBI survivors are typically managed in the intensive care unit (ICU) setting, involving invasive monitoring to measure intracranial pressure (ICP), partial pressure of oxygen in brain tissue (PbtO$_2$), and, less commonly, intracerebral flow, intracortical electroencephalogram (EEG), and microdialysis [14]. Trauma-related alterations to hemodynamics are fueled by prognostic biomarkers, coagulopathy, and cytokines such as interleukin-6 (IL-6) [15]. Coagulopathy measures such as activated partial thromboplastin time (aPTT), fibrin degradation product (D-dimer), fibrinogen, proteolytic product cleaved (C-tau) [16,17] predict long-term outcomes [18,19]. Despite maximal therapy, a large subset of patients never achieves a reasonable neurologic function. Conventional computed tomography (CT) scan in the acute phase is the cornerstone of TBI diagnosis. CT unequivocally detects lesions eligible for surgical intervention. Regardless of the GCS score after a certain threshold, an acute subdural hematoma is surgically evacuated, and in such cases "time is brain," with the prognosis improving if a patient undergoes surgery less than four hours from trauma [20]. GCS scores of 13 to 14 are categorized as mild traumatic brain injury (mTBI). mTBI is survivable and does not need hospitalization in some cases but may impact productivity [21,22]. The mTBI diagnosis is often misunderstood. Subgroups of patients are at risk of developing delayed intracranial injury (ICI) that can be catastrophic, with 25% of such patients left severely impaired or dead [23-25]. Clinical decision rules based on the Scandinavian Neurotrauma Committee (SNC), Canadian CT Head Rule (CCHR), and New Orleans Criteria (NOC) developed evidence-based guidelines to identify patients at high risk for ICI. Only recently a "Transforming Research and Clinical Knowledge in Traumatic Brain Injury" (TRACK-TBI) study, externally validated by "Collaborative European

NeuroTrauma Effectiveness Research in Traumatic Brain Injury" (CENTER-TBI), highlighted that contusion, subarachnoid hemorrhage, and/or subdural hematoma features were associated with incomplete recovery but not epidural hematoma [26]. A normal CT does not preclude brain injury and is of limited prognostic value [27,28]. The currently accepted definition of mTBI was established in 1993 by the American Congress of Rehabilitation Medicine (ACRM). Recently, a survey of an international, interdisciplinary group of clinician-scientists with expertise in mTBI identified several potential revisions to consider when updating the ACRM mTBI definition [29]. The ability to detect those patients could allow concentrating resources among the patients with chances of meaningful functional recovery. Hence, studies have been exploring alternative objective means to augment TBI diagnosis with blood tests, special brain imaging, eye movements, brain wave patterns, and portable imaging devices. This article presents the Food and Drug Administration (FDA) approval of the first blood-based biomarker test for the evaluation of mTBI in adults, along with possible ways to integrate digital biomarkers.

The need for this review was evident after the publication of our work on TBI patient samples [30] which captured some of the earliest perturbations after injury. However, despite numerous articles on TBI, biomarkers, and preclinical data, there were none describing (i) TBI diagnosis challenges, (ii) the process behind the approval of biomarkers, especially for neurotrauma, and (iii) known unknowns in TBI biomarker biology. Hence, for this foundational/scoping review, relevant recommendations listed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [31] were implemented. This was because at the time of manuscript submission there was only one FDA-approved TBI biomarker. Authors performed an electronic search of NCBI-PubMed, published between 1974 and 2022, and US FDA websites in English. The search terms included "Traumatic brain injury, Biomarkers, Neurotrauma diagnosis" excluding any references related to research in rodents and coronavirus disease 2019. Of the 277 citations, publications matching the biomarker glossary listed by the National Institutes of Health (NIH)-FDA workgroup were included.

Review

Biomarkers

The 21st Century Cures Act Section 507 specifies the process of biomarker qualification. Biomarkers are measures that can help characterize a baseline state, a disease process, or a response to treatment [32]. The US FDA and the NIH published the first version of the glossary included in the Biomarkers, EndpointS, and other Tools (BEST) resource [32]. The goal is to harmonize and clarify terms used in translational science and medical product development and to provide a common language for communication. Application aids future discussions, trial planning, and clinical decision-making. These include a proper intent of use, discovery tools, sample collection, data collection, data analysis, assay development, assay validation, clinical performance, regulatory approval, and market access evaluation before a diagnostic test can be commercialized and used clinically. Following biomarker discovery, this evaluation process would first include analytical validation to assess the accuracy and reliability of the proposed test to measure the candidate biomarker. They can be molecular, histologic, radiographic, and/or physiologic types. Biomarkers are divided into seven categories.

Each of these categories lends itself to different uses. A diagnostic biomarker can aid proper binary classification of subjects, for instance, an emergency department (ED) visitor seeking care into subgroups (outpatient versus inpatient) using an unbiased measure. The classifier boundary between subgroups must be determined by a threshold value of the measured object. The threshold can be assessed by comparing the prevalence of the biomarker in subgroups (Figure 1).
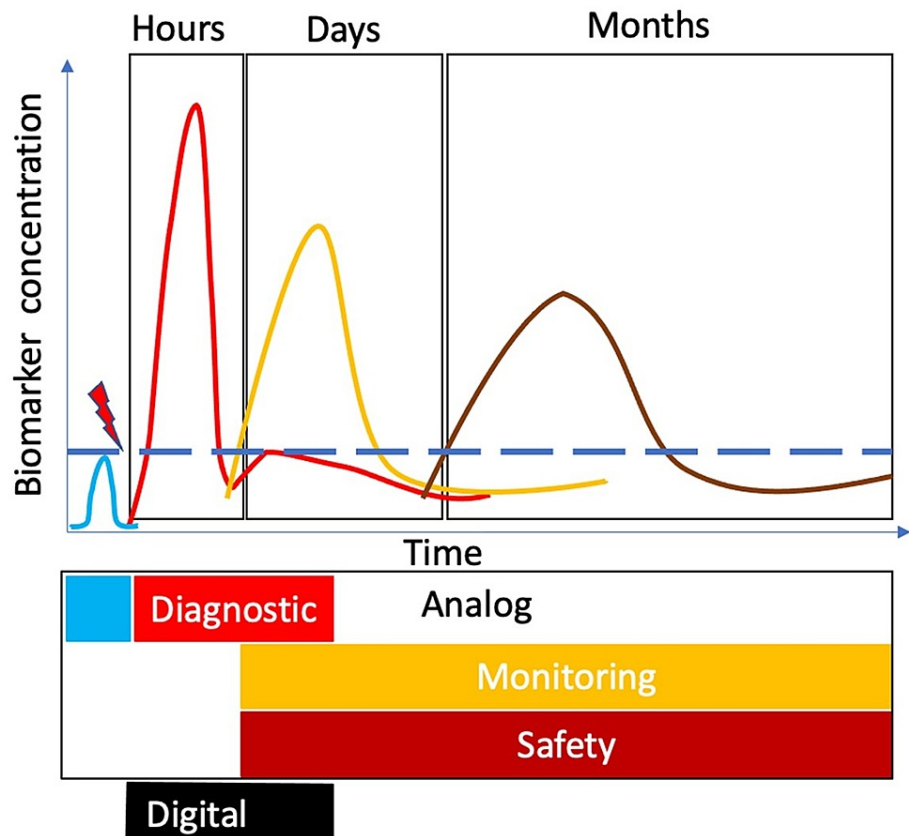
FIGURE 1: Specific biomarker types and their spatiotemporal distribution.

TBI-specific biomarker types and their spatiotemporal distribution. The prevalence of a biomarker in a healthy population (blue) shifts following injury (red thunderbolt) to a new distribution (red) above the baseline (dashed horizontal line) that is not present in 99 percentiles of the uninjured (specific to injury). Such a biomarker can peak acutely (first rectangle), function as a diagnostic biomarker, and in absence of therapy fuel a cascade of secondary injury over days and months (next to rectangles). The subsequent subacute and chronic biomarkers (yellow and brown, respectively) could serve as monitoring/therapeutic response biomarkers. Failure of therapeutic effect can be assessed by increased safety biomarker. These analog biomarkers (black outline) can be augmented with digital biomarkers (black rectangle) to detect injury and alter, especially when an individual is alone and unresponsive following TBI. It is important to reinforce that any biomarker data should be interpreted only in the context of pertinent clinical history.

TBI: traumatic brain injury

The four possible outcomes are as follows: true positive (sensitivity), true negative (specificity), false positive (type I error), and false negative (type II error). After establishing a pre-specified cutoff for the biomarker, discrimination can be assessed by the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals (CIs). The deduced positive predictive value (PPV, the probability that subjects with a positive screening test truly have the disease) and negative predictive value (NPV, the probability that subjects with a negative screening test truly do not have the disease) help assess diagnostic accuracy [33]. Before such use in the clinic, preclinical studies are required to establish the following: (i) the association of the biomarker with TBI, (ii) correlation (linear relationship) with the presence of biomarker and injury severity and prognosis, (iii) capturing evidence to attribute TBI as the most likely/sole source of the biomarker with additional causalities such as retrodictive and predictive [34]. Using such data, a requestor can approach the FDA for approval of a TBI blood biomarker through a specific program, "The Breakthrough Devices Program," part of the 21st Century Cures Act (Cures Act). This is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions [35].

Biomarkers in Neurotrauma Diagnosis

In the years before CT, neurosurgical and diagnostic interventions were often based on recognizing changes in clinical signs and symptoms. To confirm a diagnosis, the patient was subjected to a risky, invasive angiogram with a tendency to wait too long as the patient was in extremis. Consequently, TBI was

associated with high mortality rates. The existing Coma Index evolved into the Glasgow Coma Scale (GCS), which allowed earlier detection of a deteriorating patient [9,36]. TBI treatments are time-sensitive and resource-intensive [37]. An estimated 4.8 million ED visits per year are related to TBI [38-40]. The volume of work poses a substantial burden to the medical system, and this increase has been driven by a better understanding of mTBI along with interest in detecting concussion (representing a subset of mTBI without structural brain injury) early. Accurate clinical diagnosis of mTBI remains a challenge, and CT is not easily available (for instance, on the battlefield or on the pitch-side), is expensive, and imposes radiation exposure risk [41]. Hence, there is an unmet need to rapidly diagnose and manage mTBI more cost-effectively and efficiently without compromising patient care and safety. A sensitive blood-based marker that can be easily and rapidly measured in the systemic circulation would alleviate the burden imposed by the inability to diagnose TBI. Identification of biomarker signatures associated with distinct aspects of TBI pathophysiology may also be of clinical value for increasingly accurate characterization and risk stratification of TBI patients, optimizing medical decision-making, and facilitating individualized and targeted therapeutic interventions. TBI biomarkers can be distributed over the various phases post-injury, namely, acute, sub-acute, and chronic, capturing the initial damage, escalation, and progressive tissue loss [42]. Preclinical research has established the correlation and causality of TBI with induced biomarkers [43-47]. The application of proteomics in TBI research [48] accelerated the pace of TBI biomarker discovery, development, and validation. In this pioneering study, pooled naive and injured cortical samples (48-hour post-injury; male rat-controlled cortical impact model) were processed and analyzed using a differential neuroproteomics platform. Differential proteins were identified, quantitated, and confirmed. The differential proteins were categorized as: (i) decreased, (ii) increased, or (iii) putatively degraded by proteolysis. The neuronal protein ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1) was one of the proteins that increased in abundance. The preclinical study was followed by a clinical investigation of pediatric brain injury. Higher serum levels of two proteins, glial fibrillary acidic protein (GFAP) and UCH-L1, were detected in brain-injured children compared with controls. A step-wise increase in biomarker concentrations over the continuum of severity from mild to severe TBI was detected. Of the two, only the neuronal biomarker UCH-L1 had the potential to detect acute intracranial lesions, as assessed by CT. Most importantly, both markers were substantially increased in TBI patients with a normal CT. Serum UCH-L1 and GFAP concentrations also strongly predicted poor outcomes [49]. This led to the development and subsequent authorization by the US FDA of The Brain Trauma Indicator™ (BTI™), the first blood test to evaluate concussion in adults [50]. An overview of UCH-L1 and GFAP biomarkers measured by BTI™ in the blood within 12 hours post-injury is presented by Wang et al., and the turnaround time for the test is three to four hours [51]. This makes it a candidate for use in the ED or acute care setting. Levels of such biomarkers in the blood after mTBI can predict the presence of intracranial lesions in patients visible on CT scans. The TRACK-TBI study with a large prospective, multicenter, observational trial including adults (≥18 years) with head CT (part of standard emergency care) and blood collected within 12 hours of injury and prespecified cutoff values for UCH-L1 and GFAP (327 pg/mL and 22 pg/mL, respectively) reported that serum samples of 1,288 (66%) patients had a positive test result and 671 (34%) had a negative test result. The test had a sensitivity of 0.976 (95% CI = 0.931-0.995) and an NPV of 0.996 (95% CI = 0.987-0.999). In three (<1%) of the 1,959 patients, the CT scan was positive when the test was negative [52]. Recently, plasma GFAP measurements showed a high discriminative ability to predict intracranial abnormalities on CT in TBI patients across GCS 3-15 through 24-hour post-injury as a point-of-care (POC) platform prototype assay. GFAP substantially outperformed another serum biomarker, S100b [53]. Abbott Diagnostics' prototype i-STAT POC version is touted to return results in 15 minutes after the sample is placed in the cartridge, such rapid turnaround may help transferability to the clinical practice [54]. Yue et al. demonstrated that the prototype i-STAT-device determined plasma levels of GFAP within 24 hours post-injury and could discriminate between magnetic resonance imaging (MRI)-positive patients and MRI-negative patients with an area under the receiver operating characteristic (ROC) curve of 0.777 [95% CI = 0.726-0.829). Abbott Diagnostics is now partnering with the US Department of Defense and the TRACK-TBI consortium to conduct a multicenter pivotal clinical trial on the i-STAT POC version of UCH-L1/GFAP tandem plasma tests for mTBI [51]. TBI serum biomarkers were demonstrated to be of greater value over clinical characteristics in predicting CT abnormalities, with correlations to clinical severity, and care path. The study examined six serum biomarkers including GFAP. Samples were obtained <24 hours post-injury from 2,867 patients with any severity of TBI in the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) Core Study, a prospective, multicenter, cohort study. GFAP achieved the highest discrimination for predicting CT abnormalities (AUC = 0.89; 95% CI = 0.87-0.90), with a 99% likelihood of being better than clinical characteristics. Results were consistent across strata, and injury severity supported a need to develop serum GFAP assays [55]. While the findings are being independently reproduced in studies with appropriate sample size [2], and commercialization of the test is in progress, polytrauma along with mTBI poses challenges that can probably be resolved by (i) rigorous standardization of the ACRM definition of mTBI [29], and (ii) harmonizing the testing methods to reduce inter-instrument variations [56,57].

Improving TBI diagnosis with new types of biomarkers

Analog Biomarkers

The aforementioned biomarkers can be considered analog (as opposed to digital) as the test is spatiotemporally separated from the time and place of biomarker incidence in the body. The BTI™ test is run on a semi-automated enzyme-linked immunosorbent assay (ELISA) platform that requires skilled technical personnel to operate and takes three to four hours to run while i-STAT POC could cut that time in

half. Following the establishment of GFAP as the most discriminatory mTBI biomarker, molecules specific to astrocyte metabolism that are also associated with TBI could be excellent candidates. One such example is D-serine, which is a unique chirality D-handed amino acid that in physiological conditions is released by neurons to activate NMDA receptors, along with glutamate, which is important for synaptic transmission and plasticity [58,59]. Following TBI, there is a change from a phase release by neurons to a tonic glial release, which results in the hyperactivation of NMDA receptors and subsequent synaptic damage [60]. Another important anomalous phenomenon observed in TBI is dependence receptor-mediated cell death. Dependence receptors are defined as receptors that convert to pro-apoptotic death receptors following cellular stress and in the absence of ligand binding (e.g., EphB3) [30]. An extensive and thorough discussion raised important biological "known unknowns" that affect the reliability, reproducibility, and accuracy of blood-based protein biomarkers. These include (i) existence behind the blood-brain barrier, limitations imposed by the molecular size, direction of flow, and concentration gradients, half-lives in various biological fluid compartments; (ii) effect of preanalytical and analytical variables such as time, quality of sample collection, processing, and storage; and (iii) specificity and sensitivity of antibodies and existing analytical platforms [61]. In the case of proteins biomarker, digital ELISA-based multi-analyte assays could increase the sensitivity sufficient to detect a single molecule of the biomarker [42,62-64]. Similarly, nucleic acid biomarkers for TBI [65,66] detection can be improved via the adoption of the nucleic acid detection platform CRISPR-ENHANCE [67]. These approaches would complement the previously mentioned need to harmonize instrumentation and mTBI diagnostic criteria, as is being explored for imaging biomarkers [68].

Digital Biomarkers

One of the shortcomings of current biomarker studies of mTBI is reporting values at a single, and varying, post-injury time-point [61]. The availability of digital devices provides an opportunity to explore and adopt digital biomarkers as objective quantifiable measures [69,70]. Although an experimental study of intentional falls from a wheelchair among able-bodied young adults using Apple Watch showed poor sensitivity for fall detection [71], numerous anecdotes of improved outcomes from hard falls due to detection by Apple Watch consistently make the news. To assess the utility of such devices, a clinical trials (NCT04304495) GAPcare II has been initiated. It is proposed to provide insights into the feasibility, acceptability, and usability of the Apple Watch, iPhone, and the RIFitTest app for fall detection in older adults who are at high risk of recurrent falls and worse outcomes [72]. People at risk for TBI or following a TBI could use digital devices throughout their life to generate real-world data. Wearables and apps-generated collection of high-density data can give new powerful insights to rapidly respond to an incident and modulate or modify disease. Making meaningful conclusions from such data is challenging and is best addressed by artificial intelligence-based methods [61].

Table *1* discusses seven different biomarkers along with their definitions.

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	Types of biomarkers	Definition	Example in TBI	Authors
1	Susceptibility/Risk biomarker	A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or medical condition	Age, gender, occupation, everyday activities, concussion, traumatic accident involving cranial impact, apolipoprotein E polymorphism	Wang et al. (2018) [73]; Maiti et al. (2015) [74]
2	Diagnostic biomarker	A biomarker used to detect or confirm the presence of a disease or condition of interest or to identify individuals with a subtype of disease	Glasgow Coma Scale, ubiquitin C-terminal hydrolase-L1, glial fibrillary acidic protein, computed tomographic scanning, magnetic resonance imaging	Wang et al. (2021) [51]
3	Monitoring biomarker	A biomarker measured repeatedly for assessing the status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent	Cerebral metabolic rates of brain oxygen, glucose, lactate/pyruvate ratio, arterial pressure, hypotension	Toro et al. (2022) [75]
4	Prognostic biomarker	A biomarker used to identify the likelihood of a clinical event, disease recurrence, or progression in patients who have the disease or medical condition of interest	Glasgow Outcome Score, Glasgow Outcome Scale-Extended, Disability Rating Scale, blood/serum-based biomarkers	McCrea et al. (2021) [76]; Wang et al. (2018) [73]
5	Predictive biomarker	A predictive biomarker is used to identify individuals who are more likely to respond to exposure to a particular medical product or environmental agent. The response could be a symptomatic benefit, improved survival, or an adverse effect	Cerebral metabolic rates of brain oxygen. Serum biomarkers	Gan et al. (2019) [77]
6	Pharmacodynamic/Response biomarker	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent	None	Poloyac et al. (2019) [78]
7	Safety biomarker	A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate likelihood, presence, or extent of toxicity as an adverse effect	Blood, plasma, serum biomarkers, e.g., plasma neurofilament light chain, thromboelastography	Scott et al. (2017) [79]

TABLE 1: Types of biomarkers.

TBI: traumatic brain injury

Conclusions

Currently, BTI™ is the only FDA-approved biomarker in neurotrauma diagnosis. Abundant intracellular UCH-L1 and GFAP are present in neurons and astrocytes, respectively, in the brain parenchyma and are thought to be released into the body fluids by TBI. However, how they are subsequently metabolized remains unknown. Addressing such knowledge gaps in biomarker biology, standardizing mTBI inclusion criteria, and increasing detection sensitivity and assay speed can improve diagnostic accuracy which can be used for proper classification of patients. Combining the aforementioned analog biomarkers with modern digital assay platforms can shorten the interval between injury and admission to hospital. The advent of wearables will allow us to go beyond the snapshot of biomarkers in the clinic and facilitate continuous monitoring of populations at higher risk for TBI such that timely personalized intervention can be administered to prevent secondary injury (post-TBI seizures) and improve outcomes.

Additional Information

Disclosures

References

1. Dewan MC, Rattani A, Gupta S, et al.: Estimating the global incidence of traumatic brain injury . J Neurosurg. 2018, 1-18. 10.3171/2017.10.JNS17352
2. Hossain I, Mohammadian M, Takala RS, et al.: Early levels of glial fibrillary acidic protein and neurofilament light protein in predicting the outcome of mild traumatic brain injury. J Neurotrauma. 2019, 36:1551-60. 10.1089/neu.2018.5952
3. Institute of Medicine: Returning home from Iraq and Afghanistan: assessment of readjustment needs of veterans, service members, and their families. The National Academies Press, Washington, DC; 2013. 10.17226/13499
4. Menon DK, Schwab K, Wright DW, Maas AI: Position statement: definition of traumatic brain injury . Arch Phys Med Rehabil. 2010, 91:1637-40. 10.1016/j.apmr.2010.05.017
5. Faul M, Wald MM, Rutland-Brown W, Sullivent EE, Sattin RW: Using a cost-benefit analysis to estimate outcomes of a clinical treatment guideline: testing the Brain Trauma Foundation guidelines for the treatment of severe traumatic brain injury. J Trauma. 2007, 63:1271-8. 10.1097/TA.0b013e3181493080
6. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC: The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation. 2007, 22:341-53.
7. Taylor CA, Bell JM, Breiding MJ, Xu L: Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. MMWR Surveill Summ. 2017, 66:1-16. 10.15585/mmwr.ss6609a1
8. Jennett B: The history of the Glasgow Coma Scale: an interview with professor Bryan Jennett. Interview by Carole Rush. Int J Trauma Nurs. 1997, 3:114-8. 10.1016/s1075-4210(97)90005-5
9. Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G: The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol. 2014, 13:844-54. 10.1016/S1474-4422(14)70120-6
10. Corso P, Finkelstein E, Miller T, Fiebelkorn I, Zaloshnja E: Incidence and lifetime costs of injuries in the United States. Inj Prev. 2015, 21:434-40. 10.1136/ip.2005.010983rep
11. van Dijck JT, Dijkman MD, Ophuis RH, de Ruiter GC, Peul WC, Polinder S: In-hospital costs after severe traumatic brain injury: a systematic review and quality assessment. PLoS One. 2019, 14:e0216743. 10.1371/journal.pone.0216743
12. Karibe H, Hayashi T, Hirano T, Kameyama M, Nakagawa A, Tominaga T: Surgical management of traumatic acute subdural hematoma in adults: a review. Neurol Med Chir (Tokyo). 2014, 54:887-94. 10.2176/nmc.cr.2014-0204
13. Katsuki M, Kakizawa Y, Nishikawa A, Kunitoki K, Yamamoto Y, Wada N, Uchiyama T: Fifteen cases of endoscopic treatment of acute subdural hematoma with small craniotomy under local anesthesia: endoscopic hematoma removal reduces the intraoperative bleeding amount and the operative time compared with craniotomy in patients aged 70 or older. Neurol Med Chir (Tokyo). 2020, 60:439-49. 10.2176/nmc.oa.2020-0071
14. Monteiro E, Ferreira A, Mendes E, Dias CC, Czosnyka M, Paiva JA, Dias C: Brain multimodal monitoring in severe acute brain injury: is it relevant to patient outcome and mortality?. Acta Neurochir Suppl. 2021, 131:83-6. 10.1007/978-3-030-59436-7_18
15. Hergenroeder GW, Moore AN, McCoy JP Jr, Samsel L, Ward NH 3rd, Clifton GL, Dash PK: Serum IL-6: a candidate biomarker for intracranial pressure elevation following isolated traumatic brain injury. J Neuroinflammation. 2010, 7:19. 10.1186/1742-2094-7-19
16. Zemlan FP, Jauch EC, Mulchahey JJ, Gabbita SP, Rosenberg WS, Speciale SG, Zuccarello M: C-tau biomarker of neuronal damage in severe brain injured patients: association with elevated intracranial pressure and clinical outcome. Brain Res. 2002, 947:131-9. 10.1016/s0006-8993(02)02920-7
17. Solla DJ, de Amorim RL, Kolias AG, Hutchinson PJ, de Andrade AF, Teixeira MJ, Paiva WS: Incremental prognostic value of coagulopathy in addition to the crash score in traumatic brain injury patients. Neurocrit Care. 2021, 34:130-8. 10.1007/s12028-020-00991-7
18. Ost M, Nylén K, Csajbok L, et al.: Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. Neurology. 2006, 67:1600-4. 10.1212/01.wnl.0000242732.06714.0f
19. Salehpour F, Bazzazi AM, Porhomayon J, Nader ND: Correlation between coagulopathy and outcome in severe head trauma in neurointensive care and trauma units. J Crit Care. 2011, 26:352-6. 10.1016/j.jcrc.2010.12.005
20. Bullock MR, Chesnut R, Ghajar J, et al.: Surgical management of acute subdural hematomas . Neurosurgery. 2006, 58:S16-24; discussion Si-iv.
21. Boake C, McCauley SR, Pedroza C, Levin HS, Brown SA, Brundage SI: Lost productive work time after mild to moderate traumatic brain injury with and without hospitalization. Neurosurgery. 2005, 56:994-1003; discussion 994-1003.
22. Bullock MR, Merchant RE, Choi SC, Gilman CB, Kreutzer JS, Marmarou A, Teasdale GM: Outcome measures for clinical trials in neurotrauma. Neurosurg Focus. 2002, 13:ECP1. 10.3171/foc.2002.13.1.6
23. Livingston DH, Lavery RF, Passannante MR, et al.: Emergency department discharge of patients with a negative cranial computed tomography scan after minimal head injury. Ann Surg. 2000, 232:126-32. 10.1097/00000658-200007000-00018
24. Miller JD, Tocher JL, Jones PA: Extradural haematoma--earlier detection, better results. Brain Inj. 1988, 2:83-6. 10.3109/02699058809150934
25. Tauber M, Koller H, Moroder P, Hitzl W, Resch H: Secondary intracranial hemorrhage after mild head injury in patients with low-dose acetylsalicylate acid prophylaxis. J Trauma. 2009, 67:521-5; discussion 525.

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10.1097/TA.0b013e3181a7c184

26. Yuh EL, Jain S, Sun X, et al.: Pathological computed tomography features associated with adverse outcomes after mild traumatic brain injury: a TRACK-TBI study with external validation in CENTER-TBI. JAMA Neurol. 2021, 78:1137-48. 10.1001/jamaneurol.2021.2120

27. Metting Z, Rödiger LA, De Keyser J, van der Naalt J: Structural and functional neuroimaging in mild-to-moderate head injury. Lancet Neurol. 2007, 6:699-710. 10.1016/S1474-4422(07)70191-6

28. Laalo JP, Kurki TJ, Sonninen PH, Tenovuo OS: Reliability of diagnosis of traumatic brain injury by computed tomography in the acute phase. J Neurotrauma. 2009, 26:2169-78. 10.1089/neu.2009.1011

29. Silverberg ND, Iverson GL: Expert panel survey to update the American Congress of Rehabilitation Medicine definition of mild traumatic brain injury. Arch Phys Med Rehabil. 2021, 102:76-86. 10.1016/j.apmr.2020.08.022

30. Tsenkina Y, Tapanes SA, Díaz MM, et al.: EphB3 interacts with initiator caspases and FHL-2 to activate dependence receptor cell death in oligodendrocytes after brain injury. Brain Commun. 2020, 2:fcaa175. 10.1093/braincomms/fcaa175

31. Tricco AC, Lillie E, Zarin W, et al.: PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018, 169:467-73. 10.7326/M18-0850

32. Cagney DN, Sul J, Huang RY, Ligon KL, Wen PY, Alexander BM: The FDA NIH Biomarkers, EndpointS, and other Tools (BEST) resource in neuro-oncology. Neuro Oncol. 2018, 20:1162-72. 10.1093/neuonc/nox242

33. Zou G: From diagnostic accuracy to accurate diagnosis: interpreting a test result with confidence . Med Decis Making. 2004, 24:313-8. 10.1177/0272989X04265483

34. Mayeux R: Biomarkers: potential uses and limitations . NeuroRx. 2004, 1:182-8. 10.1602/neurorx.1.2.182

35. FDA U. Breakthrough Devices Program. (2021). Accessed: May 01, 2021: https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program.

36. McLatchie G, Jennett B: ABC of sports medicine. Head injury in sport . BMJ. 1994, 308:1620-4. 10.1136/bmj.308.6944.1620

37. Maas AI, Stocchetti N, Bullock R: Moderate and severe traumatic brain injury in adults . Lancet Neurol. 2008, 7:728-41. 10.1016/S1474-4422(08)70164-9

38. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019, 18:56-87. 10.1016/S1474-4422(18)30415-0

39. Korley FK, Kelen GD, Jones CM, Diaz-Arrastia R: Emergency department evaluation of traumatic brain injury in the United States, 2009-2010. J Head Trauma Rehabil. 2016, 31:379-87. 10.1097/HTR.0000000000000187

40. Peterson A, Xu L, Daugherty J, Breiding M: Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths, United States, 2014. National Center for Injury Prevention and Control, Atlanta, GA; 2019.

41. Haydel MJ, Preston CA, Mills TJ, Luber S, Blaudeau E, DeBlieux PM: Indications for computed tomography in patients with minor head injury. N Engl J Med. 2000, 343:100-5. 10.1056/NEJM200007133430204

42. Mondello S, Buki A, Barzo P, et al.: CSF and plasma amyloid-β temporal profiles and relationships with neurological status and mortality after severe traumatic brain injury. Sci Rep. 2014, 4:6446. 10.1038/srep06446

43. Czeiter E, Mondello S, Kovacs N, et al.: Brain injury biomarkers may improve the predictive power of the IMPACT outcome calculator. J Neurotrauma. 2012, 29:1770-8. 10.1089/neu.2011.2127

44. Dave JR, Williams AJ, Yao C, Lu XC, Tortella FC: Modeling cerebral ischemia in neuroproteomics . Methods Mol Biol. 2009, 566:25-40. 10.1007/978-1-59745-562-6_2

45. Kochanek PM, Bramlett HM, Shear DA, et al.: Synthesis of findings, current investigations, and future directions: operation brain trauma therapy. J Neurotrauma. 2016, 33:606-14. 10.1089/neu.2015.4133

46. Mondello S, Schmid K, Berger RP, et al.: The challenge of mild traumatic brain injury: role of biochemical markers in diagnosis of brain damage. Med Res Rev. 2014, 34:503-31. 10.1002/med.21295

47. Yao C, Williams AJ, Ottens AK, et al.: Detection of protein biomarkers using high-throughput immunoblotting following focal ischemic or penetrating ballistic-like brain injuries in rats. Brain Inj. 2008, 22:723-32. 10.1080/02699050802304706

48. Kobeissy FH, Ottens AK, Zhang Z, et al.: Novel differential neuroproteomics analysis of traumatic brain injury in rats. Mol Cell Proteomics. 2006, 5:1887-98. 10.1074/mcp.M600157-MCP200

49. Mondello S, Kobeissy F, Vestri A, Hayes RL, Kochanek PM, Berger RP: Serum concentrations of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein after pediatric traumatic brain injury. Sci Rep. 2016, 6:28203. 10.1038/srep28203

50. FDA U. FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults . (2018). Accessed: May 01, 2021: https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-first-blood-test-aid-evaluation-concussi....

51. Wang KK, Kobeissy FH, Shakkour Z, Tyndall JA: Thorough overview of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein as tandem biomarkers recently cleared by US Food and Drug Administration for the evaluation of intracranial injuries among patients with traumatic brain injury. Acute Med Surg. 2021, 8:e622. 10.1002/ams2.622

52. Bazarian JJ, Biberthaler P, Welch RD, et al.: Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. Lancet Neurol. 2018, 17:782-9. 10.1016/S1474-4422(18)30231-X

53. Okonkwo DO, Puffer RC, Puccio AM, et al.: Point-of-care platform blood biomarker testing of glial fibrillary acidic protein versus S100 calcium-binding protein B for prediction of traumatic brain injuries: a transforming research and clinical knowledge in traumatic brain injury study. J Neurotrauma. 2020, 37:2460-7. 10.1089/neu.2020.7140

54. Korley FK, Datwyler SA, Jain S, et al.: Comparison of GFAP and UCH-L1 measurements from two prototype assays: the Abbott i-STAT and ARCHITECT assays. Neurotrauma Rep. 2021, 2:193-9. 10.1089/neur.2020.0037

55. Czeiter E, Amrein K, Gravesteijn BY, et al.: Blood biomarkers on admission in acute traumatic brain injury:

2022 Nishimura et al. Cureus 14(4): e23804. DOI 10.7759/cureus.23804

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relations to severity, CT findings and care path in the CENTER-TBI study. EBioMedicine. 2020, 56:102785. 10.1016/j.ebiom.2020.102785

56. Posti JP, Hossain I, Takala RS, et al.: Glial fibrillary acidic protein and ubiquitin C-terminal hydrolase-L1 are not specific biomarkers for mild CT-negative traumatic brain injury. J Neurotrauma. 2017, 34:1427-38. 10.1089/neu.2016.4442

57. Papa L, Wang KK: Raising the bar for traumatic brain injury biomarker research: methods make a difference . J Neurotrauma. 2017, 34:2187-9. 10.1089/neu.2017.5030

58. Benneyworth MA, Li Y, Basu AC, Bolshakov VY, Coyle JT: Cell selective conditional null mutations of serine racemase demonstrate a predominate localization in cortical glutamatergic neurons. Cell Mol Neurobiol. 2012, 32:613-24. 10.1007/s10571-012-9808-4

59. Assis-Nascimento P, Tsenkina Y, Liebl DJ: EphB3 signaling induces cortical endothelial cell death and disrupts the blood-brain barrier after traumatic brain injury. Cell Death Dis. 2018, 9:7. 10.1038/s41419-017-0016-5

60. Perez EJ, Tapanes SA, Loris ZB, Balu DT, Sick TJ, Coyle JT, Liebl DJ: Enhanced astrocytic d-serine underlies synaptic damage after traumatic brain injury. J Clin Invest. 2017, 127:3114-25. 10.1172/JCI92300

61. McDonald SJ, Shultz SR, Agoston DV: The known unknowns: an overview of the state of blood-based protein biomarkers of mild traumatic brain injury. J Neurotrauma. 2021, 38:2652-66. 10.1089/neu.2021.0011

62. O'Connell GC, Alder ML, Smothers CG, Still CH, Webel AR, Moore SM: Use of high-sensitivity digital ELISA improves the diagnostic performance of circulating brain-specific proteins for detection of traumatic brain injury during triage. Neurol Res. 2020, 42:346-53. 10.1080/01616412.2020.1726588

63. Thangavelu B, Boutté AM: Single molecule assay for ultrasensitive detection of cathepsin B in human blood . ACS Omega. 2021, 6:9609-16. 10.1021/acsomega.1c00180

64. Khetani S, Singh A, Besler B, et al.: µDrop: multi-analyte portable electrochemical-sensing device for blood-based detection of cleaved tau and neuron filament light in traumatic brain injury patients. Biosens Bioelectron. 2021, 178:113033. 10.1016/j.bios.2021.113033

65. Dadas A, Washington J, Diaz-Arrastia R, Janigro D: Biomarkers in traumatic brain injury (TBI): a review . Neuropsychiatr Dis Treat. 2018, 14:2989-3000. 10.2147/NDT.S125620

66. Das Gupta S, Ciszek R, Heiskanen M, et al.: Plasma miR-9-3p and miR-136-3p as potential novel diagnostic biomarkers for experimental and human mild traumatic brain injury. Int J Mol Sci. 2021, 22:1563. 10.3390/ijms22041563

67. Nguyen LT, Gurijala J, Rananaware SR, Pizzano BL, Stone BT, Jain PK: CRISPR-ENHANCE: an enhanced nucleic acid detection platform using Cas12a [In press]. Methods. 2021, 10.1016/j.ymeth.2021.02.001

68. Rincon SP, Mukherjee P, Levin HS, et al.: Interrater reliability of National Institutes of Health traumatic brain injury imaging common data elements for brain magnetic resonance imaging in mild traumatic brain injury. J Neurotrauma. 2021, 38:2831-40. 10.1089/neu.2021.0138

69. Snyder CW, Dorsey ER, Atreja A: The best digital biomarkers papers of 2017 . Digit Biomark. 2018, 2:64-73. 10.1159/000489224

70. Omberg L, Chaibub Neto E, Perumal TM, et al.: Remote smartphone monitoring of Parkinson's disease and individual response to therapy [In press]. Nat Biotechnol. 2021, 10.1038/s41587-021-00974-9

71. Abou L, Fliflet A, Hawari L, et al.: Sensitivity of Apple Watch fall detection feature among wheelchair users [In press]. Assist Technol. 2021, 10.1080/10400435.2021.1923087

72. Strauss DH, Davoodi NM, Healy M, Metts CL, Merchant RC, Banskota S, Goldberg EM: The Geriatric Acute and Post-Acute Fall Prevention Intervention (GAPcare) II to assess the use of the Apple Watch in older emergency department patients with falls: protocol for a mixed methods study. JMIR Res Protoc. 2021, 10:e24455. 10.2196/24455

73. Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, Manley GT: An update on diagnostic and prognostic biomarkers for traumatic brain injury. Expert Rev Mol Diagn. 2018, 18:165-80. 10.1080/14737159.2018.1428089

74. Maiti TK, Konar S, Bir S, Kalakoti P, Bollam P, Nanda A: Role of apolipoprotein E polymorphism as a prognostic marker in traumatic brain injury and neurodegenerative disease: a critical review. Neurosurg Focus. 2015, 39:E3. 10.3171/2015.8.FOCUS15329

75. Toro C, Temkin N, Barber J, et al.: Association of vasopressor choice with clinical and functional outcomes following moderate to severe traumatic brain injury: a TRACK-TBI study. Neurocrit Care. 2022, 36:180-91. 10.1007/s12028-021-01280-7

76. McCrea MA, Giacino JT, Barber J, et al.: Functional outcomes over the first year after moderate to severe traumatic brain injury in the prospective, longitudinal TRACK-TBI study. JAMA Neurol. 2021, 78:982-92. 10.1001/jamaneurol.2021.2043

77. Gan ZS, Stein SC, Swanson R, Guan S, Garcia L, Mehta D, Smith DH: Blood biomarkers for traumatic brain injury: a quantitative assessment of diagnostic and prognostic accuracy. Front Neurol. 2019, 10:446. 10.3389/fneur.2019.00446

78. Poloyac SM, Bertz RJ, McDermott LA, Marathe P: Pharmacological optimization for successful traumatic brain injury drug development. J Neurotrauma. 2020, 37:2435-44. 10.1089/neu.2018.6295

79. Scott G, Zetterberg H, Jolly A, et al.: Minocycline reduces chronic microglial activation after brain trauma but increases neurodegeneration. Brain. 2018, 141:459-71. 10.1093/brain/awx339

2022 Nishimura et al. Cureus 14(4): e23804. DOI 10.7759/cureus.23804

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