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New Insights and perspectives on traumatic brain injury: Integration, translation and multidisciplinary approaches

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New Insights and perspectives on traumatic brain injury: Integration, translation and multidisciplinary approaches

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Editorial: New insights and perspectives on traumatic brain injury: integration, translation and multidisciplinary approaches

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Editorial on the Research Topic
New insights and perspectives on traumatic brain injury: integration, translation and multidisciplinary approaches

Introduction

Traumatic brain injury (TBI) remains one of healthcare's most significant challenges and policy making. TBI could not only lead to long-term functional impairment but also a decrease in quality of life. Lowering the mortality risk and benefitting survivors' living quality remains the target of neurotrauma studies globally. With the advent of novel TBI-related clinical and basic research approaches, diagnostics, therapeutics research, and novel and multidisciplinary methods have emerged. Despite promising progress, no completely effective treatment prevents or minimizes TBI and its related neurological and psychiatric sequelae. Understanding the mechanisms underlying the pathophysiology, treatment progress, and clinically based translational and engineering research on TBI may pave the way for potential treatment targets, diagnostic markers, and preventive methods that ultimately lead to efficacious therapeutic strategies. In this Research Topic, we are delighted to have received several outstanding studies focusing on various aspects of TBI-related research, which have provided us with numerous insights and inspirations. We will provide a detailed review based on the collection status of this Research Topic and the development of the field.

Perspectives

The 12 diverse research articles published on this Research Topic not only make significant contributions to integration, translation, and multidisciplinary aspects but also

essentially cover important references ranging from prevention, personalized stratification, precision treatments to prognosis. This aligns with the viewpoints proposed by The Lancet Neurology Commission on TBI (1), mutually corroborating and highlighting the significance and value of this Research Topic. They specifically include and cover the following three main aspects.

Basic and translational research

This Research Topic, focusing on basic and translational research, delves into research articles and reviews on TBI-related mechanisms and experimental methods, including the following articles: *Diffusion basis spectrum imaging detects subclinical traumatic optic neuropathy in a closed-head impact mouse model of traumatic brain injury* (Yang et al.) and *Models of traumatic brain injury-highlights and drawbacks* (Zhao et al.).

They articulate various aspects of TBI models from different perspectives. As we know, TBI is a combination of anatomical and functional damage to the brain following direct mechanical injury. The brain damage caused by TBI is a mixture of structural, cellular, and vascular damage. The structural damage caused by the initial impact activates complex molecular and cellular cascade reactions. Therefore, animal models commonly used for TBI research include fluid percussion injury (FPI), controlled cortical impact injury (CCI), weight drop impact acceleration injury (WDIAI), and blast injury models, each with their own characteristics and limitations. Further improvement and optimization of these models require more excellent research to support and corroborate (2, 3) (Zhao et al.).

In another aspect of basic research, we have also received two sets of examples from bibliometrics and scientometrics which are: *The bibliometric and altmetric analysis of chronic traumatic encephalopathy research: how great is the impact?* (Guan et al.) and *An exhaustive analysis of post-traumatic brain injury dementia using bibliometric methodologies* (Sang et al.). Scientometrics and bibliometrics are methodological approaches in which the scientific literature itself becomes the subject of analysis. There has already been a series of concentrated applications of it in clinical disease-related research (4–7). Scientometrics and bibliometrics often involve monitoring research, assessing the scientific contributions of authors, journals, or specific works, as well as analyzing the dissemination process of scientific knowledge. Additionally, several excellent reviews included in the Research Topic have provided us with new insights from multiple dimensions, including: *Advances in understanding the pathogenesis of post-traumatic epilepsy: a literature review* (Fang et al.), *Post-traumatic olfactory dysfunction: a scoping review of assessment and rehabilitation approaches* (De Luca et al.), and *History of concussion and lowered heart rate variability at rest beyond symptom recovery: a systematic review and meta-analysis* (Wesolowski et al.). These detailed and in-depth summaries and descriptions provide valuable references for us to gain a deeper understanding of TBI.

Clinical research

In this Research Topic, research articles and reviews that delve into in-depth exploration from the perspective of clinical practical issues include: *The prognostic value of an age-adjusted BIG score in adult patients with traumatic brain injury* (Bai et al.), *Chronic kidney disease as a predictive factor for poor prognosis in traumatic brain injury among older adults: a case-control study* (Mo et al.), and *Epidemiological characteristics for patients with traumatic brain injury and the nomogram model for poor prognosis: an 18-year hospital-based study* (Guo et al.) with *Secondary hyperperfusion injury following surgical evacuation for acute isolated epidural hematoma with concurrent cerebral herniation* (Huang et al.). Each one is an exciting clinical-relevant study, presenting not only the current panorama and hotspots of clinical exploration in TBI comprehensively, but also providing important research references for diagnosis, treatment, and potential applications, especially in all aspects closely related to TBI prognosis. To enrich TBI-related clinical research, methods such as expanding the sample size, increasing the number of study subjects, conducting multicenter collaborative research, strengthening clinical trials and translational research, establishing comprehensive data collection and analysis systems, and conducting real-world studies have all been increasingly utilized and have yielded beneficial research outcomes (8–13).

Forensic and precision identification research

In the field of TBI research, another important area is forensic and precision identification research, which intersects closely with disciplines such as early biomarker discovery, functional assessment, and imaging. In this domain, the identification of mild traumatic brain injury (mTBI) is particularly crucial. mTBI often presents with mild clinical symptoms and subtle imaging findings, making it prone to misdiagnosis or underdiagnosis, especially when the severity of injury does not necessarily correlate with the degree of post-injury functional impairment. To address these challenges in forensic clinical and judicial practice, numerous scholars have provided important research directions, including exploration of biomarkers, studies on rapid detection methods, in-depth exploration of medical imaging, and interdisciplinary research based on deep learning artificial intelligence (14–21). Including the research article *Translational medical bioengineering research of traumatic brain injury among Chinese and American pedestrians caused by vehicle collision based on human body finite element modeling* (Yan et al.), in this Research Topic, It is also an important interdisciplinary translational study with relevance to forensic identification. In this research domain, there is a need to explore more early potential biomarkers of mTBI, develop sensitive and rapid multimodal identification methods, and ultimately provide a solid theoretical foundation and practical basis for the resolution of forensic precision identification issues.

Conclusion and final considerations

The goal of this Research Topic is to disseminate high-quality research on traumatic brain injury (TBI) and related fields, with a particular focus on comprehensive and in-depth studies involving integration, translation, and multidisciplinary approaches. The aim is to bridge the gap between basic neuroscience knowledge and the unmet needs in brain health through these methodologies. To achieve this, the Research Topic presents a collection of compelling research studies and reviews that showcase advancements in neuroscience and explore multidisciplinary and interdisciplinary integration. We hope that this Research Topic will contribute to advancing the understanding of this complex and multifaceted field. However, beyond the research content and insights provided by this Research Topic, we must also acknowledge that the complexity of different perspectives often results in the omission of the service provision system, which encompasses prevention, pre-hospital and hospital care, rehabilitation, and resocialization of the disabled. This omission is closely related to the role of public health and the quality of services provided in accordance with evidence-based medicine. Addressing these aspects would enhance the impact of the contribution by mobilizing the professional community in support of TBI victims. Therefore, additional aspects should be considered. These include developing comprehensive strategies for the prevention of TBI, improving pre-hospital care protocols to ensure timely and effective initial treatment, enhancing hospital care with cutting-edge medical practices, and establishing robust rehabilitation programs that focus on both physical and cognitive recovery. Additionally, creating supportive environments for the resocialization of disabled individuals is crucial. By incorporating these elements, we can create a holistic approach that not only advances scientific understanding but also significantly improves patient outcomes and quality of life for TBI sufferers.

We hope that this Research Topic will contribute to advancing the understanding of this complex and multifaceted field. We extend our heartfelt gratitude to the various groups that submitted their scientific findings to this Research Topic, as well as to the reviewers who generously dedicated their time, effort, and expertise to enhance the quality of each study.

Author contributions

JS: Writing – original draft, Writing – review & editing. ZZ: Writing – review & editing. XD: Writing – original draft, Writing – review & editing. MC: Writing – review & editing. JC: Writing – original draft, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Maas AI, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol.* (2022) 21:1004–60. doi: 10.1016/S1474-4422(22)00307-6

2. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. *Nat Rev Neurosci.* (2013) 14:128–42. doi: 10.1038/nrn3407

3. Kundu S, Singh S. What happens in TBI? A wide talk on animal models and future perspective. *Curr Neuropharmacol.* (2023) 21:1139. doi: 10.2174/1570159X20666220706094248

4. Shi J, Du X, Cavagnaro MJ, Li N. A bibliometric analysis and visualization of the top-cited publications in mild traumatic brain injury. *Front Neurol.* (2021) 12:687796. doi: 10.3389/fneur.2021.687796

5. Mojgani P, Jalali M, Keramatfar A. Bibliometric study of traumatic brain injury rehabilitation. *Neuropsychol Rehabil.* (2022) 32:51–68. doi: 10.1080/09602011.2020.1796714

6. Liao Z, Wei W, Yang M, Kuang X, Shi J. Academic publication of neurodegenerative diseases from a bibliographic perspective: a comparative scientometric analysis. *Front Aging Neurosci.* (2021) 13:722944. doi: 10.3389/fnagi.2021.722944

7. Qu M, Xu Y, Lu L. Global research evolution and frontier analysis of artificial intelligence in brain injury: a bibliometric analysis. *Brain Res Bull.* (2024) 5:110920. doi: 10.1016/j.brainresbull.2024.110920

8. Nelson LD, Temkin NR, Dikmen S, Barber J, Giacino JT, Yuh E, et al. Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: a transforming research and clinical knowledge in traumatic brain injury (TRACK-TBI) study. *J Am Med Assoc Neurol.* (2019) 76:1049–59.

9. Ahmed Z. Current clinical trials in traumatic brain injury. *Brain Sci.* (2022) 12:527. doi: 10.3390/brainsci12050527

10. Nordström A, Nordström P. Traumatic brain injury and the risk of dementia diagnosis: a nationwide cohort study. *PLoS Med.* (2018) 15:e1002496. doi: 10.1371/journal.pmed.1002496

11. Steyerberg EW, Wiegers E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol.* (2019) 18:923–34.

12. Schwenkreis P, Gonschorek A, Berg F, Meier U, Rogge W, Schmehl I, et al. Prospective observational cohort study on epidemiology, treatment and outcome of patients with traumatic brain injury (TBI) in German BG

hospitals. *Br Med J Open.* (2021) 11:e045771. doi: 10.1136/bmjopen-2020-045771

13. Shi J, Teng J, Du X, Li N. Multi-modal analysis of resting-state fMRI data in mTBI patients and association with neuropsychological outcomes. *Front Neurol.* (2021) 12:639760. doi: 10.3389/fneur.2021.639760

14. Kim HJ, Tsao JW, Stanfill AG. The current state of biomarkers of mild traumatic brain injury. *JCI Insight.* (2018) 3:97105. doi: 10.1172/jci.insight.97105

15. Li X, Han L, Guo Y, Chang Y, Yan J, Wang Y, et al. Rapid detection and cellular fluorescence imaging of the TBI biomarker Let-7i using a DNA-AgNC nanoprobe. *N J Chem.* (2019) 43:7997–8004. doi: 10.1039/C9NJ00489K

16. Khetani S, Singh A, Besler B, Butterworth S, Lijnse T, Loughery K, 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 Bioelectr.* (2021) 178:113033. doi: 10.1016/j.bios.2021.113033

17. Pankratova N, Jović M, Pfeifer ME. Electrochemical sensing of blood proteins for mild traumatic brain injury (mTBI) diagnostics and prognostics: towards a point-of-care application. *RSC Adv.* (2021) 11:17301–19. doi: 10.1039/D1RA00589H

18. Li N, Cavagnaro MJ, Xiong K, Du X, Shi J. The multi-modal risk analysis and medical prevention of lumbar degeneration, fatigue, and injury based on FEM/BMD for elderly Chinese women who act as stay-home grandchildren sitters. *Front Publ Health.* (2021) 9:700148. doi: 10.3389/fpubh.2021.700148

19. Wei W, Li N, Du X, Sun Z, Chen W, Rong P, et al. Rapid prediction and accurate location selection of mild traumatic brain injury (mTBI) by using multiple parameter analysis of diffusion tensor imaging (DTI): integrating correlational and clinical approaches. *BioMed Res Int.* (2023) 2023:7467479. doi: 10.1155/2023/7467479

20. Teng J, Liu W, Mi C, Zhang H, Shi J, Li N. Extracting the most discriminating functional connections in mild traumatic brain injury based on machine learning. *Neurosci Lett.* (2023) 810:137311. doi: 10.1016/j.neulet.2023.137311

21. Shang Y, Wang Y, Guo Y, Ren L, Zhang X, Wang S, et al. Analysis of the risk of traumatic brain injury and evaluation neurogranin and myelin basic protein as potential biomarkers of traumatic brain injury in postmortem examination. *For Sci Med Pathol.* (2022) 18:288–98. doi: 10.1007/s12024-022-00459-4

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Secondary hyperperfusion injury following surgical evacuation for acute isolated epidural hematoma with concurrent cerebral herniation

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Objective: Hemispherical cerebral swelling or even encephalocele after head trauma is a common complication and has been well elucidated previously. However, few studies have focused on the secondary brain hemorrhage or edema occurring regionally but not hemispherically in the cerebral parenchyma just underneath the surgically evacuated hematoma during or at a very early stage post-surgery.

Methods: In order to explore the characteristics, hemodynamic mechanisms, and optimized treatment of a novel peri-operative complication in patients with isolated acute epidural hematoma (EDH), clinical data of 157 patients with acute-isolated EDH who underwent surgical intervention were reviewed retrospectively. Risk factors including demographic characteristics, admission Glasgow Coma Score, preoperative hemorrhagic shock, anatomical location, and morphological parameters of epidural hematoma, as well as the extent and duration of cerebral herniation on physical examination and radiographic evaluation were considered.

Results: It suggested that secondary intracerebral hemorrhage or edema was determined in 12 of 157 patients within 6h after surgical hematoma evacuation. It was featured by remarkable, regional hyperperfusion on the computed tomography (CT) perfusion images and associated with a relatively poor neurological prognosis. In addition to concurrent cerebral herniation, which was found to be a prerequisite for the development of this novel complication, multivariate logistic regression further showed four independent risk factors contributing to this type of secondary hyperperfusion injury: cerebral herniation that lasted longer than 2h, hematomas that were located in the non-temporal region, hematomas that were thicker than 40mm, and hematomas occurring in pediatric and elderly patients.

Conclusion: Secondary brain hemorrhage or edema occurring within an early perioperative period of hematoma-evacuation craniotomy for acute-isolated EDH is a rarely described hyperperfusion injury. Because it plays an important prognostic influence on patients' neurological recovery, optimized treatment should be given to block or reduce the consequent secondary brain injuries.

KEYWORDS

acute epidural haematoma, brain herniation, cerebrovascular autoregulation, reperfusion injury, secondary brain injury

Introduction

Isolated acute epidural hematoma (EDH) is one of the most common intracranial injuries, accounting for 2.7–11% of all intracranial injury cases (1). Though timely surgical intervention usually achieves satisfactory outcomes (2), some potential complications can still seriously affect the prognosis (3, 4). Among these complications, intracerebral hemorrhage or edema caused by hyperperfusion during or shortly after surgery causes special attention due to its high mortality and disability (5). However, few studies have reported its characteristics and risk factors. In this study, we retrospectively analyzed patients with isolated EDH who underwent craniotomy in our hospital. Those with intracerebral hemorrhage or edema were identified, and their characteristics were reported in order to have a better understanding of this complication.

Methods

Participants

This retrospective study was based on patients admitted into our department between June 2009 and May 2020. The diagnosis was confirmed by the head trauma history, clinical presentations, and radiological findings. The inclusion criteria were as follows: (1) isolated supratentorial EDHs confirmed by computed tomography (CT); (2) patients with cerebral herniation; and (3) patients who underwent craniotomy or decompressive craniectomy. The exclusion criteria were as follows: (1) those with severe heart, lung, and other systemic diseases; (2) those with serious brain contusion and laceration, subdural hematoma, and primary brain stem injury; (3) those with infratentorial EDH or EDH straddling the transverse sinus; (4) those with secondary cerebral infarction; and (5) patients who had incomplete clinical data, including the 3-month follow-up. The research was reviewed and approved by the Institutional Review Board of the 909th Hospital, School of Medicine, Xiamen University.

Clinical management

A head CT scan was performed for all patients after admission. Those who were suspected of having a risk of secondary brain injury would receive an additional CT angiography (CTA) and CT perfusion (CTP) examination. A craniotomy or a decompressive craniectomy was performed as soon as possible if necessary. Postsurgical management included intracranial pressure (ICP) monitoring, seizure prophylaxis, and nutritional support. Tracheal intubation and mechanical ventilation were adopted based on patients' consciousness and arterial oxygen saturation.

Radiographic evaluation

Patients received regular CT examinations before and 1, 3, and 7 days after surgery. CT images were evaluated by two independent senior neuroradiologists with the assistance of clinical neurosurgeons. Diffusion-weighted imaging/apparent diffusion coefficient/magnetic resonance imaging (DWI/ADC-MRI) was applied to confirm if there were *de novo* low-dense lesions in the secondary hyperperfusion.

Neurological outcomes at follow-ups

Patients were followed at 1 and 3 months after discharge with CT imaging and physical examinations. Thereafter, follow-ups were performed either by telephone interview or by outpatient examination at an interval of 6 months. Neurological outcome was evaluated by using the glasgow outcome scale (GOS) as follows: I, death; II, vegetative survival in a long-term coma; III, severe disability needing care providers; IV, mild disability, being able to take care of daily life; and V, good outcomes, with adults being able to work and study.

Statistical analysis

Collected data included age, gender, and GCS score upon admission. Data distribution was evaluated by histogram and the Kolmogorov–Smirnov test. Continuous data were either expressed as mean ± standard deviation (SD, statistical analysis: Student's *t*-test) or median and interquartile range (IQR, statistical analysis: Mann–Whitney *U*-test). Categorical variables were analyzed by the Pearson χ^2 or Fisher exact test. Parameters with a *p*-value of less than 0.2 in the univariate analysis were included in the multivariable logistic regression analysis. All the statistical analyses were performed with SPSS, and a *p*-value of less than 0.05 was considered to be statistically significant.

Results

In total, 157 patients with isolated supratentorial EDHs who had craniotomy or decompressive craniectomy in our department between June 2009 and May 2020 were included in our study. There were 134 (85.35%) male patients and 23 (14.65%) female patients, with a mean age of 35.20 ± 14.58 years. The injury mechanism included traffic accidents (120/157), assault injuries (19/157), and falling injuries (18/157). The hematoma was located in the temporal area in 89 (56.69%) cases, and in the non-temporal areas, it was seen in 68 (43.31%) cases. Preoperative unilateral pupil dilation was found in 127 (80.89%) cases and bilateral pupil dilation in 30 (19.11%) cases. The mean duration of brain herniation was 73.7 ± 36.6 min, and the mean GCS on admission was 7.30 ± 2.32 points.

Diffusion-weighted/apparent diffusion coefficient magnetic resonance imaging (DWI/ADC-MRI) and CTP examinations were performed to clarify whether the secondary brain hemorrhage or edema was an ischemic lesion or hyperperfusion lesion. Among the 206 patients, 12 cases were found to have secondary hemorrhage or edema, confirmed with hyperperfusion by CTP (Table 1), while another 145 were indicated to have normal cerebral perfusion. The characteristics of patients with a hyperperfusion lesion and normal cerebral perfusion are

TABLE 1 CTP parameters of 12 patients with secondary brain hemorrhage or edema due to hyperperfusion.

CTP parameters	hyperperfusion lesion region	Contralateral mirror region	*p*-value
CBF[mL/(100 g.min)]	67.43 ± 7.48	43.98 ± 5.00	<0.001
CBV[mL/100 g]	5.31 ± 0.64	3.82 ± 0.47	<0.001
MTT(s)	2.72 ± 0.38	3.40 ± 0.42	<0.001

CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time.

presented in Table 2. Patients with a hyperperfusion lesion had a lower GCS score, longer duration of preoperative herniation, larger EDH volume and thickness, and were more likely to have non-temporal EDH location compared to those with normal perfusion. In the multivariable logistic regression analysis, the duration of preoperative herniation and EDH thickness were independently associated with the risk of hyperperfusion injury (Table 3).

Patients with hyperperfusion injury had significantly worse clinical outcomes compared to those with normal perfusion (3-month GOS score, 3.83 vs. 4.89, $p = 0.011$; Table 4). Among the 12 patients with hyperperfusion injury, two had unresponsive wakefulness (GOS 2), three had a severe disability (GOS 3), two had a mild disability (GOS 4), and five had a good recovery (GOS 5) at a 3-month follow-up.

Case 1

As shown in Figure 1, a 12-year-old boy was admitted with hemorrhagic shock after a traffic accident (GCS 5). Physical

TABLE 2 Clinical characteristics of patients with normal perfusion and hyperperfusion.

Clinical parameters	Risk stratification	Normal perfusion	Hyperperfusion	*P*-value
n (%)		145	12	-
Sex	Female	26 (89.66)	3 (10.34)	0.465
	Male	119 (92.97)	9 (7.03)	
Age (year)	-	34.94 ± 14.59	37.67 ± 20.42	0.549
	12–65	138 (93.88)	9 (6.12)	0.030
	≤12 or ≥65	7 (70.00)	3 (30.00)	
Shock	No	135 (92.47)	11 (7.53)	0.595
	Yes	10 (90.91)	1 (9.09)	
GCS	-	7.99 ± 2.05	6.33 ± 0.98	<0.001
	≤5	10 (90.91)	1 (9.09)	0.595
	≥6	135 (92.47)	11 (7.53)	
Duration of preoperative herniation (min)	-	60.14 ± 24.87	115.00 ± 44.21	<0.001
	<60	74 (97.37)	2 (2.63)	<0.001
	60–120	66 (94.29)	3 (4.35)	
	≥120	5 (41.67)	7 (58.33)	
Admission pupil state	Unilateral dilation	137 (93.20)	10 (6.80)	0.171
	Bilateral dilation	8 (80.00)	2 (20.00)	
Basal cistern	Narrowed	106 (92.98)	8 (7.02)	0.737
	Disappeared	39 (90.70)	4 (9.30)	
Midline shift (mm)	-	10.58 ± 2.23	11.83 ± 1.19	0.057
	<10	39 (97.50)	1 (2.50)	0.446
	≥10	106 (90.60)	11 (9.40)	
EDH location	Non-temporal	65 (86.67)	10 (13.33)	0.014
	Temporal	80 (97.56)	2 (2.44)	
EDH volume (mL)	-	89.83 ± 29.50	114.08 ± 31.62	0.007
	<120	123 (95.35)	6 (4.65)	0.008
	≥120	22 (78.57)	6 (21.43)	
EDH diameter (cm)	-	9.18 ± 1.28	8.58 ± 1.12	0.113
	<10	103 (90.35)	11 (9.65)	0.229
	≥10	42 (97.67)	1 (2.33)	
EDH thickness (mm)	-	29.70 ± 6.27	39.50 ± 6.20	<0.001
	<35	120 (97.56)	3 (2.44)	<0.001
	35–40	15 (88.24)	2 (11.76)	
	≥40	10 (58.82)	7 (41.18)	

EDH, epidural hematoma; GCS, glasgow coma scale.

TABLE 3 Multivariate logistic regression analysis for the risk of secondary reperfusion injury following surgical evacuation of acute EDH.

Clinical factors	Risk stratification	Partial regression coefficient	Relative risk (95% CI)	*P*-value
Duration of preoperative herniation, min	60–120	1.230	3.422 (0.481–24.349)	0.219
	≥120	4.121	61.617 (5.851–648.890)	0.001
EDH thickness, mm	35–40	1.084	2.956 (0.289–30.239)	0.361
	≥40	2.308	10.051 (1.478–68.366)	0.018
Age, yr	<12或>65	1.744	5.723 (0.633–51.770)	0.121
EDH location	Non-temporal	1.706	5.507 (0.734–41.306)	0.097

EDH, epidural hematoma.

TABLE 4 Clinical outcomes in the included patients (%).

Clinical parameters	Risk stratification	Normal perfusion	Hyperperfusion	*P*-value
n (%)	-	145 (70.39)	12 (5.83)	-
3-Month GOS	-	4.89 ± 0.47	3.83 ± 1.19	0.011
	1	0	0	<0.001
	2	0	2 (16.67)	
	3	2 (1.38)	3 (25.00)	
	4	9 (6.21)	2 (16.67)	
	5	134 (92.41)	5 (41.67)	

GOS, glasgow outcome scale.

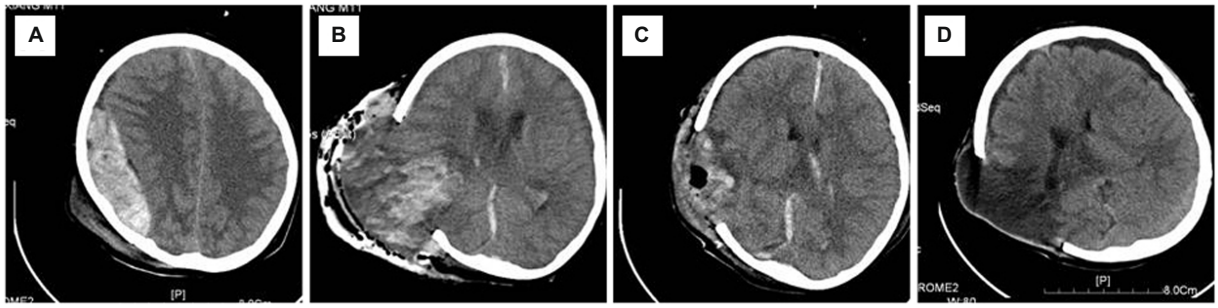

FIGURE 1
Representative radiographic images of Case 1. **(A)** An acute epidural hematoma in the right temporal–parietal area; **(B)** regional but not hemispherical bulging of the brain tissue occurred after hematoma evacuation, and intra-operative CT confirmed that there was no remote or contralateral hematoma except a "flame"-like intraparenchymal hemorrhage in the hematoma-compressed area; **(C)** incarcerated and necrotic cerebral parenchyma was resected, and the remaining brain tissue became atonic; **(D)** 1-month CT follow-up showed the presence of a focal encephalomalacia in the affected area and a contralateral subdural effusion, without any remote cerebral infarction. CT, computerized tomography.

examination showed right pupil dilation (5 mm) and left pupil fixation (3 mm). Emergency CT depicted an acute epidural hematoma in the right temporal-parietal area with a volume of 83 ml and a thickness of 31 mm. After a preoperative emergency burr hole draining of the epidural hematoma, the right pupil returned to 4 mm but was re-dilated to 5 mm after 10 min. The duration of cerebral herniation before the initiation of surgery was estimated to be approximately 150 min based on the first-aid records and surgical files. During the intraoperative evacuation of the hematoma, dural tension increased sharply, and the underneath brain tissue bulged out rapidly after the incision of the dura mater. Intraoperative CT showed a "flame"-shaped intracerebral hemorrhage in the involved brain tissue. After downregulating blood pressure, hyperventilation, and controlled cold compression onto the surgical area and the administration of large-dose steroids, the brain tissue was softened to some extent but remained herniated outside the craniotomy defect. Therefore, the herniated brain tissue had to be dissected. This patient scored 3 points on the Glasgow Outcome Scale at the 12-month follow-up and had left hemiplegia with decreased muscle strength (grade III).

Case 2

A 35-year-old man fell from a high place and was admitted with an acute EDH in the right frontoparietal area with a volume

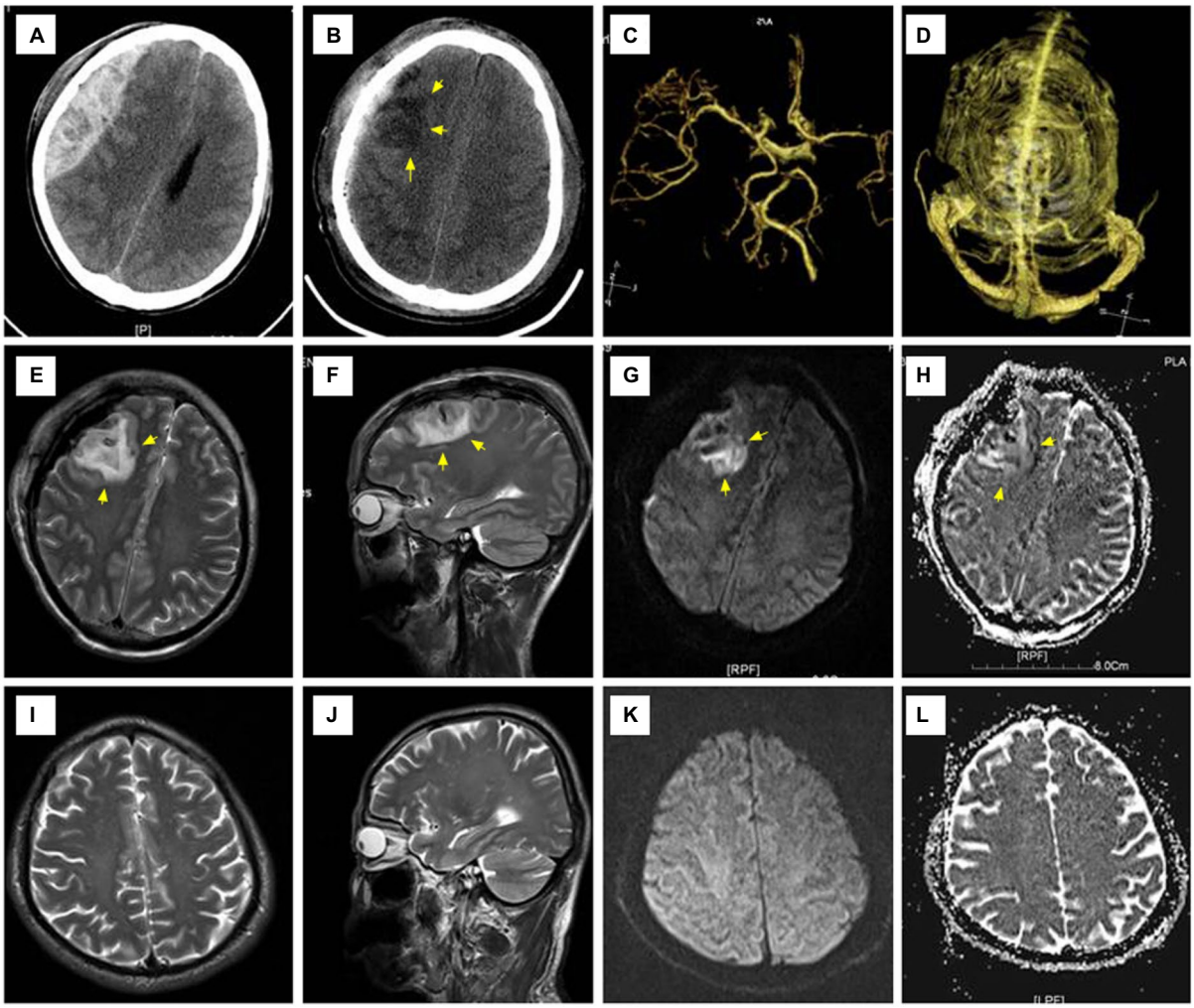

FIGURE 2
Representative radiographic images of Case 2. **(A)** An acute epidural hematoma occupying the right frontoparietal area; **(B)** CT examination performed 3h after surgery showed patchy cerebral edema mixed with a few spotty areas of hemorrhage in the right frontal lobe; **(C,D)** CTA and CTV showed no obvious abnormalities; **(E–H)** T2WI showed a small amount of intracerebral hemorrhage and edema in the right frontal lobe with high signal on both DWI and ADC; **(I–L)** MRI re-examination 1month after surgery showed that the lesion disappeared and the involved brain tissue recovered. CTA, CT angiography; CTV, CT venography; T1WI:T1 weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; MRI, magnetic resonance imaging.

of 118 ml and a thickness of 30 mm (Figure 2). Admission examination showed a 5-mm right pupil and a 3-mm left pupil. The patient scored seven points on the GCS scale, and the duration of herniation was estimated to be approximately 160 min. There was no preoperative shock. Preoperative burr hole drainage was performed. After surgical hematoma evacuation, the underlying dura mater showed a mild collapse; however, the tension was endurable, so the dura mater was not incised. CT examination performed 3 h later after surgery showed patchy cerebral edema mixing with a small amount of intraparenchymal hemorrhage at the compressed area. MRI examination showed signs of reperfusion injury in the right frontal lobe. Conservative treatment was effectual for the postoperative management of intracranial pressure, and no secondary surgery was required. This patient had a satisfactory recovery without any neurological dysfunction and scored five points on the GOS at the last follow-up 24 months later.

Case 3

A 44-year-old man was admitted with an acute EDH in the right parietal-occipital area that was 144 ml in volume and 41 mm in thickness (Figure 3). Admission physical examination found that he had a 5-mm dilated right pupil and a 3-mm fixed-left pupil. This patient scored 4 points on the GCS scale, and the duration of herniation was estimated to be approximately 150 min before surgery. There was no preoperative shock. The dural pressure increased gradually after intra-operative hematoma evacuation. Intra-operative CT showed patchy areas of cerebral edema in the hematoma-compressed parenchyma and simultaneous CBF showed increased perfusion in the right occipital lobe. Intraoperative ICP management techniques were performed, including raising the head position, covering the focal dura mater with cold gauze, steroid administration, dehydration intervention, and hyperventilation. After those interventions, the tension of the dura mater stabilized, and, thus, it was

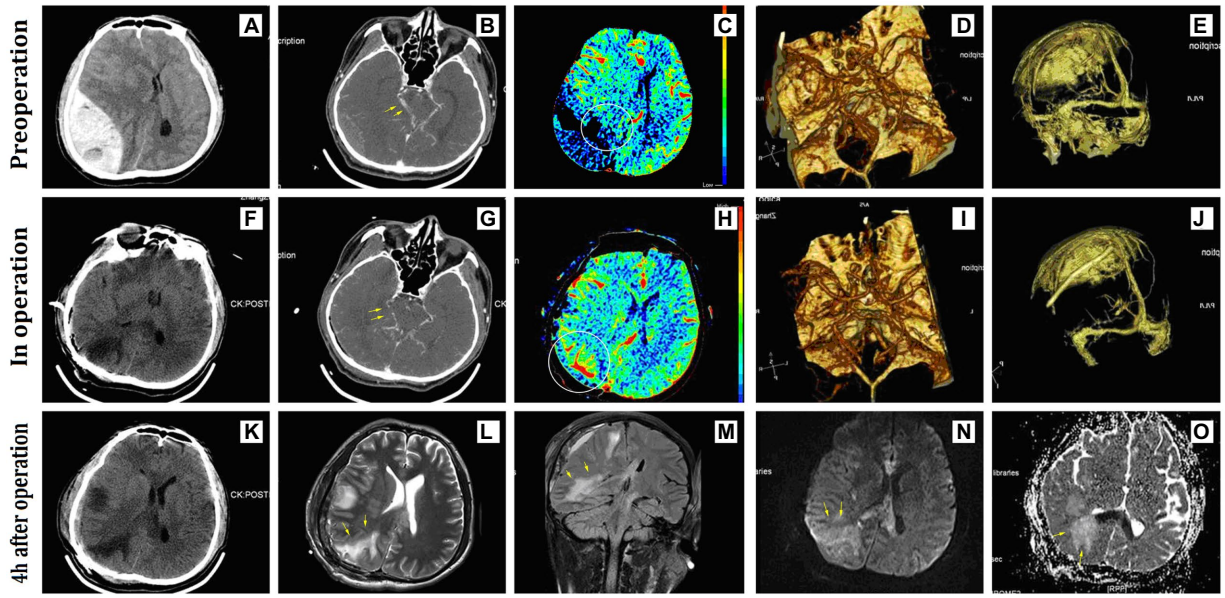

FIGURE 3
Representative radiographic images of Case 3. **(A)** A huge acute epidural hematoma occupied the right parietal-occipital area; **(B–D)** preoperative CTA showed compression and displacement of the right posterior cerebral artery; **(C)** preoperative CBF showed low perfusion due to hematoma compression in the right occipital lobe; **(E–J)** no significant compression on the venous sinus before and after surgery; **(F–K)** intra- and postoperative CT showed a low-density lesion in the right occipital lobe; **(G–I)** intra-operative CTA showed lessened displacement of the posterior cerebral artery; **(H)** intra-operative CBF showed increased perfusion in the right occipital lobe; **(L–M)** MRI examination performed 4h after surgery showed long-signal shadows in the compressed areas of the right occipital lobe and corpus callosum on T2WI and FLAIR sequence; **(N,O)** the right occipital lobe showed long-signal on the DWI sequence and ADC sequence. CBF, cerebral blood flow; FLAIR, fluid-attenuated inversion recovery.

not incised. This patient had a satisfactory recovery without an additional decompressive craniectomy and scored 4 points on the GOS scale at the last follow-up 18 months after discharge.

Discussion

A patient who has an isolated EDH without severe intraparenchymal injury at the time of head injury usually recovers satisfactorily after timely and effective treatment (6). The largest prognostic threat comes from the development and progression of secondary brain injury induced predominantly by the mechanical compression of the epidural hematoma (7, 8), which calls for effectual pre-hospital first aid and a meticulous and well-organized surgical plan. In this study, we reported intracerebral hemorrhage or edema that occurs during surgical decompression or in the early post-surgical stage. We postulated that the underlying mechanism of this secondary brain injury might involve the impairment of cerebrovascular autoregulation of the decompensated intracranial vessels and the consequent focal hyperperfusion (9–12). The results showed that although the incidence of hyperperfusion injury is relatively low, it usually leads to unfavorable outcomes compared to those with normal perfusion.

The autoregulation function gets impaired during the early stage of a craniocerebral injury (13, 14), especially when CBF decreased markedly or hemodynamic disturbance occurred. As a result, dysfunction of cerebrovascular autoregulation becomes an important factor contributing to secondary brain injury in the early post-injury period (15). The mass effect of huge epidural hematoma directly compresses the underlying brain tissues and reduces blood perfusion to certain degrees, thereby producing a pathological basis of potential secondary brain injury. Because the ability of vasodilation of cerebral blood vessels is much greater than vasoconstriction (65 vs. 8–10% of the baseline caliber), it produces a greater influence on cerebral perfusion (16, 17). After hematoma evacuation, blood vessels in the locally compressed area are in an extreme state of tension restoration (10), which inevitably causes excessive brain blood reperfusion (18–20). Our study found that the secondary hemorrhage and edema in the brain parenchyma after surgical decompression were more pronounced in the area of direct compression, and their distribution was highly identical to the previous description.

Cerebral blood flow of intracranial vessels in the area directly compressed by hematoma was decreased markedly, where the local metabolic microenvironment underwent changes and progressively became worse with continued compression (21, 22). It indicated that the autoregulation function of the intracranial vessels involved is severely impaired, and the possibility of a fatal CBF burst following decompression and perfusion restoration is increasing gradually, which may even cause local congestive edema or hemorrhage. This justifies the rational supposition that the duration of brain herniation is a risk factor, as demonstrated in the current study. As longitudinal compression has the most pronounced impact on cortical branches, perforating branches of the intracranial vessels, and their communication (23, 24), it may involve higher-grade and more feeding arteries, eventually causing more pronounced and extensive injury to the autoregulatory function of the intracranial vessels. It is therefore theoretically reasonable to consider hematoma thickness as a risk factor for abnormal reperfusion injury. As the autoregulatory function of intracranial vessels in children and the elderly is either not well developed or decreased in compliance (25, 26), they are unable

to make proper regulations to protect against abnormal hyperperfusion. In such patients who live, the course of the disease is usually short, the total volume of hematoma is relatively small, pressing time for vessels is transient, and the impairment to the autoregulation function of the blood vessels is relatively mild, therefore, reperfusion-induced secondary injury is also relatively mild.

Compared with the aforementioned uncontrollable influencing factors, we first notice that the amplitude of instant change in CBF reperfusion is controllable to some extent. It is also an important factor affecting CBF reperfusion in patients with abnormal cerebral vascular autoregulation (27–29). Tamaki et al. (30) found that the quick evacuation of the hematoma could decrease the intracranial pressure sharply and, at the same time, trigger a severe aggravation of hemodynamic change, thus worsening the overload injury to the decompensated cerebral vessels. Based on this understanding, they advanced the concept of the gradual evacuation of intracranial hematoma to avoid instant vigorous fluctuations of intracranial pressure and CBF reperfusion. To the best of our knowledge, we are the first to point out pathological mechanisms of vigorous change in CBF reperfusion during the process of EDH evacuation. Based on this finding, we also propose a therapeutic strategy to control the amplitude of CBF during instant cerebral blood reperfusion, which is expected to reduce the occurrence of abnormal reperfusion injury. For this reason, we make use of the core idea of controlled decompression and have made some beneficial explorations and practices in our neurological center with satisfactory clinical outcomes (31). First, we conducted a preliminary skull drilling to suction a portion of the EDH for moderate decompression before the formal craniotomy when managing patients with cerebral herniation from a huge epidural hematoma. The process can not only release fatal compression on the brain stem quickly and shorten the duration of cerebral herniation but also ensure stable gradient release of intracranial pressure by controlling the amount and rate of hematoma drainage. It is also useful to control the amplitude of instant change of CBF reperfusion in the decompressed area and attenuate the second strike on the local cerebral vessels in which autoregulatory ability has been impaired, thus creating an opportunity to prevent abnormal reperfusion injury following the decompression procedures. Second, to assess the cause of increased dural tension during decompression and especially differentiate it from intracranial hypertension due to distal hemorrhage, subdural hematoma formation, and venous reflux dysfunction to avoid the disastrous consequence from decompression by imprudent incision of the dura mater, we used the mobile CT scanner (NeuroLogica, USA) for intra-operative examination to exclude the latter causes and then raised the head position during surgery, covered the local dura with ice saline, and employed steroids, dehydration, and hyperventilation without opening the dura. Such patients often achieved satisfactory therapeutic outcomes with these techniques. In high-risk patients who are preoperatively assessed as having abnormal reperfusion injury, timely postoperative CT, CTP, or even MRI scanning re-examinations are often necessary. Even in patients who need a second craniotomy, surgical time should be assessed correctly. Above all, abnormal reperfusion injury during EDH evacuation can be minimized by positive pretreatment, which will eventually improve the clinical outcome.

Our study has several limitations that should be accounted for. Due to the retrospective nature of the study, conclusions related to risk factors for prediction should be taken with caution. Furthermore, allowing for rarity, the sample was slightly inadequate, and several patients were lost to follow-up adding to the weaknesses of the analysis. Consequently, an insufficiently detailed statistical analysis was conducted to interpret the possible factors that appeared to influence the prediction.

In summary, abnormal reperfusion injury following EDH evacuation is a common surgical complication that plays an extremely important role in restricting the surgical outcome. A further study in exploring the underlying pathological mechanism and contributing factors is crucial for perfecting the surgical plan and improving the surgical outcome.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WH, W-hW, and JL contributed to the conception and design of the study. YZ organized the database. FL performed the statistical analysis. WH wrote the first draft of the manuscript. W-hW, FL, L-SH, and J-ML wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Yang C, Hui J, Xie L, Feng J, Jiang J. Comparative effectiveness of different surgical procedures for traumatic acute epidural haematoma: study protocol for prospective, observational real-world treatments of AEDH in large-scale surgical cases (PORTALS-AEDH). *BMJ Open*. (2022) 12:e051247. doi: 10.1136/bmjopen-2021-051247

2. Maugeri R, Anderson DG, Graziano F, Meccio F, Visocchi M, Iacopino DG. Conservative vs. surgical Management of Post-Traumatic Epidural Hematoma: a case and review of literature. *Am J Case Rep*. (2015) 16:811–7. doi: 10.12659/AJCR.895231

3. Wang WH, Hu LS, Lin H, Li J, Luo F, Huang W, et al. Risk factors for post-traumatic massive cerebral infarction secondary to space-occupying epidural hematoma. *J Neurotrauma*. (2014) 31:1444–50. doi: 10.1089/neu.2013.3142

4. Zhang S, Wang S, Wan X, Liu S, Shu K, Lei T. Clinical evaluation of post-operative cerebral infarction in traumatic epidural haematoma. *Brain Inj*. (2017) 31:215–20. doi: 10.1080/02699052.2016.1227088

5. Otani N, Takasato Y, Masaoka H, Hayakawa T, Yoshino Y, Yatsushige H, et al. Surgical outcome following a decompressive craniectomy for acute epidural hematoma patients presenting with associated massive brain swelling. *Acta Neurochir Suppl*. (2010) 106:261–4. doi: 10.1007/978-3-211-98811-4_49

6. Bricolo AP, Pasut LM. Extradural hematoma: toward zero mortality. A prospective study. *Neurosurgery*. (1984) 14:8–12. doi: 10.1227/00006123-198401000-00003

7. Ciurea AV, Tascu A, Brehar FM, Nuteanu L, Rizea R. A life threatening problem in infants: supratentorial epidural hematoma. *J Med Life*. (2009) 2:191–5.

8. Xiao B, Ma MY, Duan ZX, Liu JG, Chen RP, Mao Q. Could a traumatic epidural hematoma on early computed tomography tell us about its future development? A multi-center retrospective study in China. *J Neurotrauma*. (2015) 32:487–94. doi: 10.1089/neu.2013.3297

9. Gross PM, Heistad DD, Strait MR, Marcus ML, Brody MJ. Cerebral vascular responses to physiological stimulation of sympathetic pathways in cats. *Circ Res*. (1979) 44:288–94. doi: 10.1161/01.RES.44.2.288

10. Osol G, Halpern W. Myogenic properties of cerebral blood vessels from normotensive and hypertensive rats. *Am J Phys*. (1985) 249:H914–21. doi: 10.1152/ajpheart.1985.249.5.H914

11. Pannier JL, Weyne J, Leusen I. Effects of changes in acid-base composition in the cerebral ventricles on local and general cerebral blood flow. *Eur Neurol*. (1971) 6:123–6. doi: 10.1159/000114479

12. Claassen J, Thijssen D, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev*. (2021) 101:1487–559. doi: 10.1152/physrev.00022.2020

13. Hlatky R, Valadka AB, Robertson CS. Intracranial pressure response to induced hypertension: role of dynamic pressure autoregulation. *Neurosurgery*. (2005) 57:917–23. doi: 10.1227/01.NEU.0000180025.43747.fc

14. Trofimova S, Trofimov A, Dubrovin A, Agarkova D, Trofimova K, Dobrzeniecki M, et al. Assessment of cerebral autoregulation in the Perifocal zone of a chronic subdural hematoma. *Acta Neurochir Suppl*. (2021) 131:51–4. doi: 10.1007/978-3-030-59436-7_11

15. Zipfel J, Hockel KL, Gerbig I, Heimberg E, Schuhmann MU, Neunhoeffer F. Impaired autoregulation following resuscitation correlates with outcome in pediatric patients: a pilot study. *Acta Neurochir Suppl*. (2021) 131:97–101. doi: 10.1007/978-3-030-59436-7_21

16. Preiksaitis A, Krakauskaite S, Petkus V, Rocka S, Chomskis R, Dagi TF, et al. Association of Severe Traumatic Brain Injury Patient Outcomes with Duration of cerebrovascular autoregulation impairment events. *Neurosurgery*. (2016) 79:75–82. doi: 10.1227/NEU.0000000000001192

17. Rangel-Castilla L, Gasco J, Nauta HJ, Okonkwo DO, Robertson CS. Cerebral pressure autoregulation in traumatic brain injury. *Neurosurg Focus*. (2008) 25:E7. doi: 10.3171/FOC.2008.25.10.E7

18. Crippa IA, Creteur J, Smielewski P, Taccone FS, Czosnyka M. Delay of cerebral autoregulation in traumatic brain injury patients. *Clin Neurol Neurosurg*. (2021) 202:106478. doi: 10.1016/j.clineuro.2021.106478

19. Svedung Wettervik T, Howells T, Hillered L, Rostami E, Lewén A, Enblad P. Autoregulatory or fixed cerebral perfusion pressure targets in traumatic brain injury: determining which is better in an energy metabolic perspective. *J Neurotrauma*. (2021) 38:1969–78. doi: 10.1089/neu.2020.7290

20. Schmidt EA, Czosnyka M, Steiner LA, Balestreri M, Smielewski P, Piechnik SK, et al. Asymmetry of pressure autoregulation after traumatic brain injury. *J Neurosurg*. (2003) 99:991–8. doi: 10.3171/jns.2003.99.6.0991

21. Robertson CS, Goodman JC, Grossman RG. Blood flow and metabolic therapy in CNS injury. *J Neurotrauma*. (1992) 9:S579–94.

22. Sharma HS, Muresanu DF, Lafuente JV, Nozari A, Patnaik R, Skaper SD, et al. Pathophysiology of blood-brain barrier in brain injury in cold and hot environments: novel drug targets for neuroprotection. *CNS Neurol Disord Drug Targets*. (2016) 15:1045–71. doi: 10.2174/1871527315666160902145145

23. Djulejić V, Marinković S, Milić V, Georgievski B, Rašić M, Aksić M, et al. Common features of the cerebral perforating arteries and their clinical significance. *Acta Neurochir*. (2015) 157:1393. doi: 10.1007/s00701-015-2462-0

24. Liebeskind DS, Caplan LR. Intracranial arteries—anatomy and collaterals. *Front Neurol Neurosci*. (2016) 40:1–20. doi: 10.1159/000448264

25. Melamed E, Lavy S, Bentin S, Cooper G, Rinot Y. Reduction in regional cerebral blood flow during normal aging in man. *Stroke*. (1980) 11:31–5. doi: 10.1161/01.STR.11.1.31

26. Petkus V, Preiksaitis A, Chaleckas E, Chomskis R, Zubaviciute E, Vosylius S, et al. Optimal cerebral perfusion pressure: targeted treatment for severe traumatic brain injury. *J Neurotrauma*. (2020) 37:389–96. doi: 10.1089/neu.2019.6551

27. Kasprowicz M, Czosnyka M, Poplawska K, Reinhard M. Cerebral arterial time constant recorded from the MCA and PICA in Normal subjects. *Acta Neurochir Suppl*. (2016) 122:211–4. doi: 10.1007/978-3-319-22533-3_42

28. Zeiler FA, Aries M, Czosnyka M, Smielewski P. Cerebral autoregulation monitoring in traumatic brain injury: an overview of recent advances in personalized medicine. *J Neurotrauma*. (2022) 39:1477–94. doi: 10.1089/neu.2022.0217

29. Small C, Lucke-Wold B, Patel C, Abou-Al-Shaar H, Moor R, Mehkri Y, et al. What are we measuring? A refined look at the process of disrupted autoregulation and the limitations of cerebral perfusion pressure in preventing secondary injury after traumatic brain injury. *Clin Neurol Neurosurg*. (2022) 221:107389. doi: 10.1016/j.clineuro.2022.107389

30. Tamaki T, Node Y, Yamamoto Y, Teramoto A. Cardiopulmonary hemodynamic changes during acute subdural hematoma evacuation. *Neurol Med Chir (Tokyo)*. (2006) 46:219–25. doi: 10.2176/nmc.46.219

31. Chen T, Qian X, Zhu J, Yang LK, Wang YH. Controlled decompression attenuates compressive injury following traumatic brain injury via TREK-1-mediated inhibition of necroptosis and Neuroinflammation. *Oxidative Med Cell Longev*. (2021) 2021:4280951–17. doi: 10.1155/2021/4280951

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Epidemiological characteristics for patients with traumatic brain injury and the nomogram model for poor prognosis: an 18-year hospital-based study

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Objective: Traumatic brain injury (TBI) is a global social, economic, and health challenge that is associated with premature death and long-term disability. In the context of rapid development of urbanization, the analysis of TBI rate and mortality trend could provide abundant diagnosis and treatment suggestions, which helps to form future reference on public health strategies.

Methods: In this study, as one of major neurosurgical centers in China, we focused on the regime shift of TBI based on 18-year consecutive clinical data and evaluated the epidemiological features. In our current study, a total of 11,068 TBI patients were reviewed.

Results: The major cause of TBI was road traffic injuries (44.%), while the main type of injury was cerebral contusion (n = 4,974 [44.94%]). Regarding to temporal changes, a decreasing trend in TBI incidence for patients under 44 years old was observed, while an increasing trend for those aged over 45 years was indicated. Incidences of RTI and assaults decreased, while ground level fall presented increasing incidences. The total number of deaths was 933 (8.43%), with a decreasing trend in overall mortality since 2011. Age, cause of injury, GCS at admission, Injury Severity Score, shock state at admission, trauma-related diagnoses and treatments were significantly associated with mortality. A predictive nomogram model for poor prognosis was developed based on patient's GOS scores at discharge.

Conclusions: The trends and characteristics of TBI patients changed with rapid development of urbanization in the past 18 years. Further larger studies are warranted to verify its clinical suggestions.

KEYWORDS

epidemiology, traumatic brain injury, clinical characteristics, mortality, prognostic nomogram

Introduction

Globally, more than 50 million people suffer from traumatic brain injury (TBI) each year (1, 2), and it is the leading cause of death and disability for all ages (3). Annually, TBI is estimated to cost the global economy approximately US$400 billion. There is an urgent need to focus on the prevention, treatment, and research of TBI to reduce the burden and social cost (4, 5).

As a developing economical entity, China has experienced rapid urbanization in the past decades, which has had great influences on every aspect of social-economical activities, especially the medical system. Data from several large population-based studies conducted in the 1980's showed that TBI incidences in China were much lower than that in high-income countries, reflecting the incomplete demographics of Chinese patients with TBI (6). Over time, changes have occurred in the TBI landscape in China (5–9). In terms of treatment methods, a national emergency and critical care campaign has been started since the outbreak of SARS in 2003, together with the advancement of legislation, optimized emergency treatment policies, and clinical management (5–10). In 2020, the basic characteristics of TBI and the level of trauma treatment in China have been reported, indicating great advancements in the past decades (9). However, considering the imbalanced development of China, elucidation of the characteristics of different regions and exploration of the regularities behind urbanization is still needed to guide future TBI treatment, especially in developing countries.

The essence of emergency neurotrauma care is rapid assessment, decision-making, and treatment. It has been limited due to a lack of objective standard guidelines and validated risk factor models for poor prognosis to predict the outcomes of interest (11). The establishment of predictive models for patients with TBI could enhance the speed of the decision-making process for patients, families, and healthcare professionals with objective treatments (12).

In our current study, we retrospectively retrieved data over the past 18 years from 11,068 patients with TBI in a tertiary neurosurgical center in western China and analyzed the demographic characteristics, trends, death, and prognosis. A prediction nomogram model for poor prognosis was developed based on Glasgow Outcome Scale (GOS) scores for patients discharged from the hospital, which may help guide future treatment and decision-making for patients with TBI.

Materials and methods

Study design and patient selection

In this study, 11,068 patients with TBI who were treated at the Neurosurgery Trauma Center, Tangdu Hospital, Xi'an, from 1 January 2003 to 31 December 2020, were retrieved for retrospective assessment. The inclusion criteria were as follows: i. patients with TBI with confirmed brain injury, either at emergency department (ED) examination or other hospital examination within 24 h after brain injury and ii. patients with definite brain injury, multiple injuries, or decreased consciousness.

The exclusion criteria were as follows: i. penetrating brain injury and related spinal cord injury; ii. lactating and pregnant women; iii. patients with other malignant tumors, severe mental disorders, or hematological diseases; iv. patients who died in the emergency department; and v. patients with a history of neurosurgery, which may affect the judgment of the brain trauma condition.

This study adhered to the principles of the Declaration of Helsinki. All medical records were anonymized, and no patient information was extracted except for research purposes. The Institutional Research Board of Tangdu Hospital, The Fourth Military Medical University, approved this study (TDLL-202207-08).

Data source

All eligible patients were reviewed by two researchers. The demographic variables, causes of injury, clinical features, and prognosis (including death) data at admission were recorded for subsequent analysis.

Based on age, patients were divided into the following 4 groups: i. 0–14 years; ii. 15–44 years; iii. 45–64 years; and iv. over 65 years. The number of patients among groups was compared. According to the Glasgow Coma Scale (GCS), TBI severity was divided into the following three levels: i. mild—GCS scores of 13 to 15; ii. moderate—GCS scores of 9 to 12; and iii. severe—GCS scores of 3 to 8 (13). Extracranial trauma injury was quantified by the injury severity score (ISS) as follows: ISS scores of 1 to 8 denoted mild to moderate injury, ISS scores of 9 to 15 denoted serious injury, ISS scores of 16 to 24 denoted severe injury, and ISS scores of 25 to 75 denoted critical injury (14).

The causes of injury included road traffic injuries (RTI), falls from heights (FFH), ground-level falls (GLF), assaults, and others (violence and attempted suicide). RTI refers to personal injuries as a result of the motor vehicle and non-motor vehicle accidents in squares, public parking lots, and other places that are used for public passage. FFH refers to brain injuries due to falling from a high place (above the ground) and being impacted by high speed in daily work or life. GLF refers to head injuries due to accidentally falling on the ground. Assault refers to injuries that arise as a result of hitting a limb with a fist, foot, or instrument.

Definition of clinical diagnosis and treatment

Clinical diagnoses were made according to the patient's state of consciousness, vital signs, and CT scan findings. These diagnoses included cerebral contusion (CC), traumatic subarachnoid hemorrhage (T-SAH), acute subdural hematoma (A-SDH), skull fractures (including the base of skull fractures, SF), acute epidural hematoma (A-EDH), diffuse axial cord injury (DAI), and others (scalp trauma and intracranial infection). The concomitant diagnosis refers to TBI accompanied by injury to other

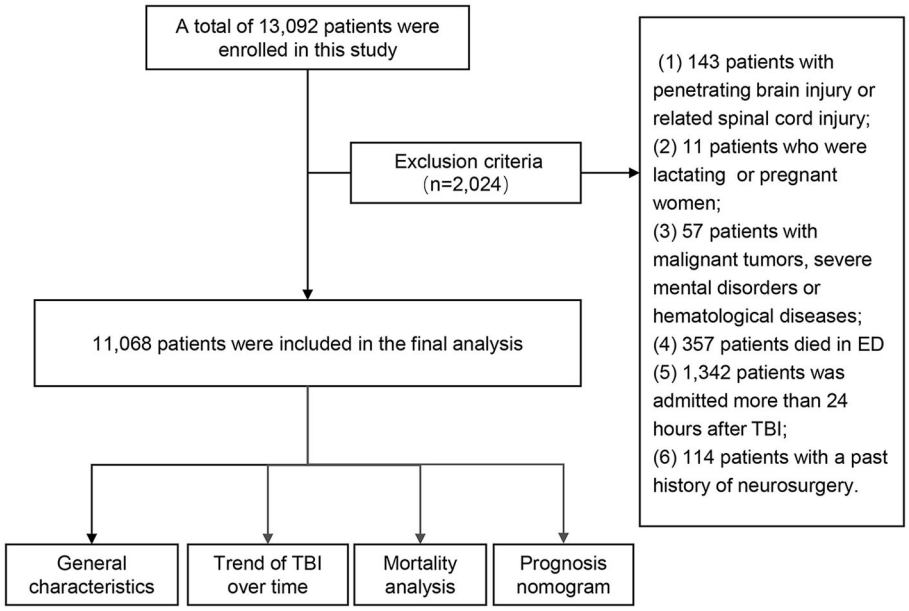

FIGURE 1
Diagram of the study procedure. TBI, traumatic brain injury; ED, emergency department.

parts of the body, including chest injury, limb injury, and others (abdominal injury and pelvic fractures).

Based on medical interventions, patients were divided into non-surgical and surgical groups. The surgical group was further divided into the following three subgroups based on surgical manipulation type: intracranial pressure (ICP) sensor insertion, craniotomy (CR), decompression craniectomy (DC), and others [external ventricular drainage (EVD) and reduction of skull fracture].

The GOS prognosis scores for all patients were determined at discharge and defined as follows: GOS scores of 1–3 denoted poor prognosis (including death), while GOS scores of 4–5 denoted good prognosis.

The nomogram prediction model

We established a nomogram prediction model for poor prognosis. Using "rms" in R, univariate and multivariate logistic regression analyses with stepwise backward were performed to screen the risk factors associated with poor prognosis. To obtain comparable odds ratios (ORs) for linear relationships and to attain clear threshold values for continuous variables, each variable was rescaled using the receiver operating characteristic (ROC) curve. Logistic regression models were established by including the risk factors, with poor prognosis as the prediction. Based on existing data, patients were randomly assigned to training and experimental groups. Patients (89.89%, n = 9,949) from 2003 to 2017 were assigned to the training cohort, while patients (10.11%, n =1,119) from 2018 to 2020 were taken as the validation cohort. There was no significant difference between the two cohorts (Supplementary Table 1). Optimal model selection was performed by applying a backward stepwise selection procedure. A nomogram was constructed based on risk factors from the multivariate logistic regression test. The nomogram's prediction accuracy was evaluated by calibration curve analyses. Finally, the model was externally validated in a separate cohort.

Statistical analyses

Descriptive statistics were used to characterize categorical and numerical variables. Categorical data were tabulated and presented as number(s) and percentage(s). Non-parametric/continuous variables (age, total length of stay, GCS, and ISS) were presented as medians and interquartile ranges (IQR), while categorical variables such as sex, causes of injury, type of injury, and survival status were presented as numbers and percentages. Univariate (chi-square test, t-test, or Mann-Whitney U test, as appropriate) and multivariate logistic regression analyses were used to analyze clinical variables associated with death to identify risk factors. Analyses were performed using IBM Statistical Package for Social Sciences (SPSS), version 23, and RStudio (1.0.136), and a p-value of $\leq$0.05 was the threshold for statistical significance.

Results

A total of 13,092 patients were enrolled in this study. Due to insufficient parameters for certain cases, 2,024 patients were excluded. Finally, 11,068 patients were included in the final analysis (Figure 1).

10.3389/fneur.2023.1138217

TABLE 1 Demographic and general characteristics of the patients in the study.

Demographic characteristics		Overall (n = 11,068)
Sex	Male	8,529 (77.06%)
	Female	2,539 (22.94%)
Age (years)	Median	43 (IQR 25–56)
	Mild	40 (IQR 22–55)
	Moderate	45 (IQR 25–56)
	Severe	46 (IQR 30–58)
	0–14 years	1,302 (11.76%)
	15–44 years	4,595 (41.52%)
	45–64 years	3,860 (34.88%)
	Over 64 years	1,311 (11.84%)
ICU length (d)	Median	2 (IQR 0–5)
Total length of stay (d)	Median	10 (IQR 5–16)
	Mild	9 (IQR 6–14)
	Moderate	11 (IQR 7–18)
	Severe	10 (IQR 3–19)
	≤1 d	776 (7.01%)
	1–7 d	2,967 (26.79%)
	7–14 d	3,898 (35.19%)
	14–30 d	2,610 (23.56%)
	>30 d	825 (7.45%)
Clinical presentation		
Cause of injury	Road traffic injuries	4,921 (44.46%)
	Falls from heights	1,731 (15.64%)
	Falls from the ground	2,626 (23.73%)
	Assaults	1,016 (9.18%)
	Other	774 (6.99%)
GCS score at admission	Median	14 (IQR 12–15)
	Mild (13–15)	4,506 (40.71%)
	Moderate (9–12)	3,150 (28.46%)
	Severe (3–8)	3,412 (30.83%)
ISS score at admission	Median	15 (IQR 9–24)
	Mild to moderate (1–8)	2,154 (19.46%)
	Serious (9–15)	3,836 (34.66%)
	Severe (16–25)	3,458 (31.24%)
	Critical (25–75)	1,624 (14.67%)
Diagnosis	CC	4,974 (44.94%)
	T-SAH	4,711 (42.56%)
	A-SDH	3,123 (28.22%)
	SF	2,324 (21.00%)
	A-EDH	2,087 (18.86%)
	DAI	353 (3.19%)
	Other	1,121 (12.15%)
Concomitant diagnosis	Total	5,617 (50.75%)
	Chest injuries	1,362 (12.31%)
	Limb injuries	1,178 (10.64%)
	Other	3,077 (27.80%)
Shock	Shock	1,014 (9.16%)
	Non-shock	10,054 (90.84%)
Treatment	Non-surgical	5,427 (49.03%)
	Surgical	5,641 (50.97%)
Surgical manipulation type	ICP	871 (15.44%)
	CR	1,627 (28.84%)
	DC	111 (1.97%)
	ICP + CR	287 (5.09%)
	ICP + DC	342 (6.06%)
	CR + DC	1,031 (18.28%)
	ICP + CR + DC	418 (7.41%)
	Other (EVD, Reduction of skull fracture)	954 (16.91%)

GCS, Glasgow Coma Scale; ISS, injury severity score; CC, cerebral contusion; T-SAH, traumatic subarachnoid hemorrhage; A-SDH, acute subdural hematoma; SF, skull fractures (including the base of skull fractures); A-EDH, acute epidural hematoma; DAI, diffuse axial cord injury; ICP, intracranial pressure sensor insertion; CR, craniotomy; DC, decompression craniectomy; EVD, external ventricular drainage.

Demographic and general characteristics

Most of the patients were male (77.06%; n = 8,529), with a median age of 43 years (IQR 25–56). Common causes of TBI were RTI, FFH, and GLF (44.46, 23.73, and 15.64%, respectively). The median GCS score at admission was 14 (IQR 12–15), of which 3,412 (30.83%) patients presented with severe TBI (GCS 3–8). The median ISS score at admission was 15 (IQR 9–24), with 1,624 (14.67%) patients presenting critical trauma (ISS 25–75). The most common diagnosis was CC (44.94%, n = 4,974), followed by T-SAH (42.56%, n = 4,711) and A-SDH (28.22%; n = 3,123). Concomitant diagnosis with TBI was frequently observed (50.75%, n = 5,617), with chest injuries being the most common (12.31%, n = 1,362). A total of 5,641 (50.97%) patients were treated with surgical interventions, with CR (28.84%, n = 1,627) being the most common surgical approach. The demographic and general characteristics of the patients are summarized in Table 1 and Figure 2A. The age group, causes of injury, severity at admission, and severity at the discharge of patients with TBI are illustrated in Figure 2B. The onset time of patients with TBI showed certain regularity in the month, week, and day (Supplementary Figure 1).

The TBI-related trend over 18 years

During 2003–2020, the total number of inpatients, gender, and mortality rates per year exhibited dynamic variations, while

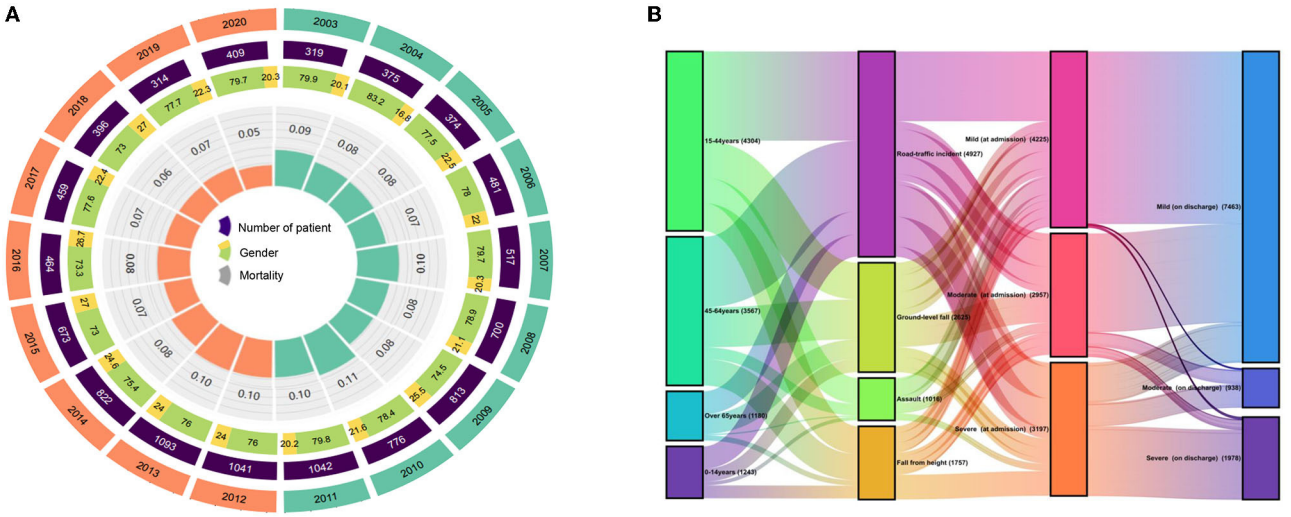

FIGURE 2
(A) Demographic and general characteristics of the patients. **(B)** Changes between age, cause of injury, severity at admission, and severity at discharge in patients with TBI.

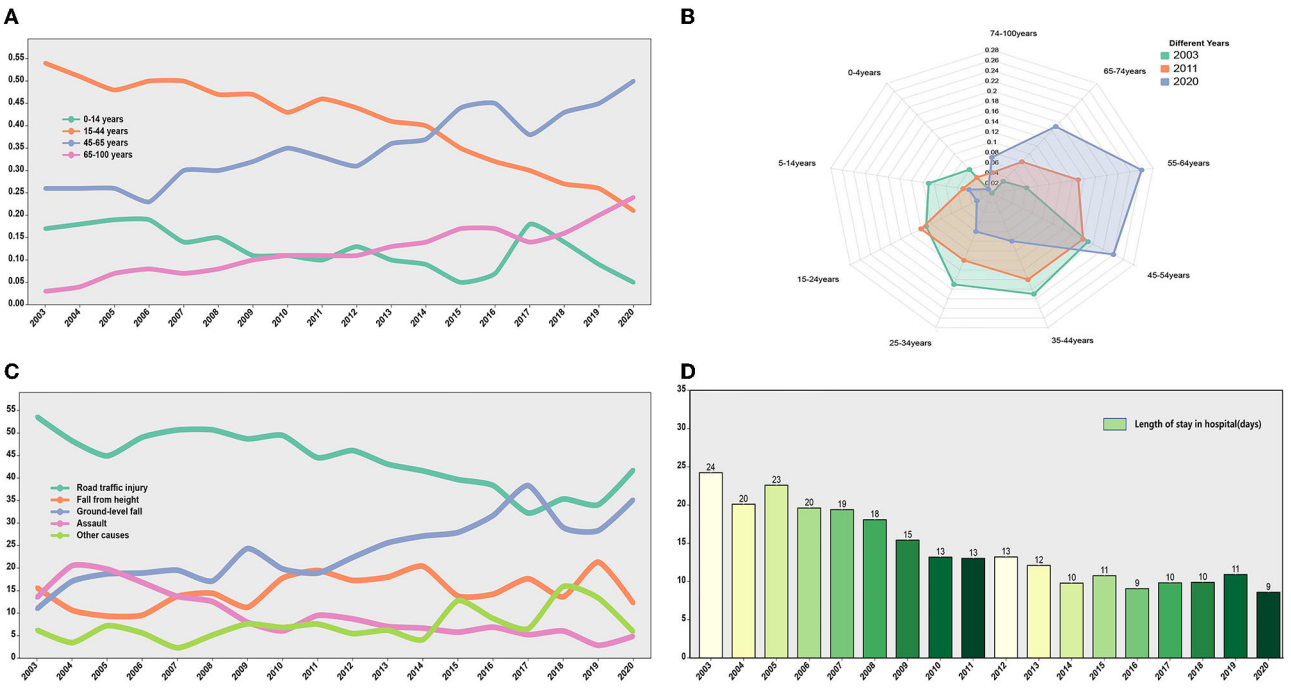

FIGURE 3
The TBI-related trend over 18 years. **(A)** The trend of TBI incidence rate over time in different age groups. The proportion of TBI incidence in age groups younger than 44 years showed a downward trend. The proportion of TBI incidence in age groups older than 44 years showed an upward trend. **(B)** The distribution of TBI age groups in different years (2003, 2011, and 2020). **(C)** The trend of injury mechanisms over time. **(D)** Length of stay in hospital (days) over time.

mortality rates slightly increased from 2003 to 2011 and thereafter significantly decreased (Figure 2A). The decrease in mortality rates might be attributed to changes in treatment modalities. For instance, the death rate has markedly reduced since the introduction of ICP sensor insertion in 2011.

From 2003 to 2020, the general characteristics of patients with TBI showed a certain trend over time. The trend was more pronounced for age, cause of injury, and length of hospital stay. We found that the proportions of TBIs in two age groups below 44 years decreased and the proportions of TBIs in two age groups above 45 years increased, especially in patients over 65 years of age (Figure 3A). The distribution of patients with TBI in different age groups varied greatly in different years. Compared with 2003, the population with the disease in 2020 is getting older (Figure 3B).

TABLE 2 Univariate and multivariate analyses between the first 9 years and the last 9 years.

		Univariate analyses		Multivariate analyses	
		P-value	OR (95% CI)	*P*-value	OR (95% CI)
GCS score at admission	Mild (13–15)	Ref	Ref	Ref	Ref
	Moderate (9–12)	0.001	0.769 (0.701–0.842)	0.001	0.681 (0.614–0.755)
	Severe (3–8)	0.001	1.2 (1.098–1.313)	0.667	1.024 (0.919–1.14)
ISS score at admission	Mild to moderate (1–8)	Ref	Ref	Ref	Ref
	Serious (9–15)	0.001	0.657 (0.591–0.731)	0.001	0.79 (0.704–0.887)
	Severe (16–25)	0.57	0.969 (0.87–1.08)	0.042	0.879 (0.777–0.995)
	Critical (over 25)	0.072	1.127 (0.99–1.283)	0.073	0.836 (0.688–1.017)
Cause of injury	Road traffic injuries	Ref	Ref	Ref	Ref
	Falls from heights	0.001	1.399 (1.254–1.562)	0.001	1.455 (1.289–1.641)
	Falls from the ground	0.001	1.759 (1.597–1.937)	0.001	1.781 (1.641–1.982)
	Assaults	0.001	0.653 (0.568–0.751)	0.001	0.703 (0.602–0.82)
	Other	0.001	1.536 (1.318–1.791)	0.001	1.492 (1.261–1.766)
Treatment	Non-surgical	Ref	Ref	Ref	Ref
	Surgical	0.001	2.206 (2.044–2.38)	0.001	1.786 (1.631–1.954)
Prognosis	Good prognosis	Ref	Ref	Ref	Ref
	Poor prognosis	0.001	0.836 (0.76–0.92)	0.001	1.388 (1.19–1.619)

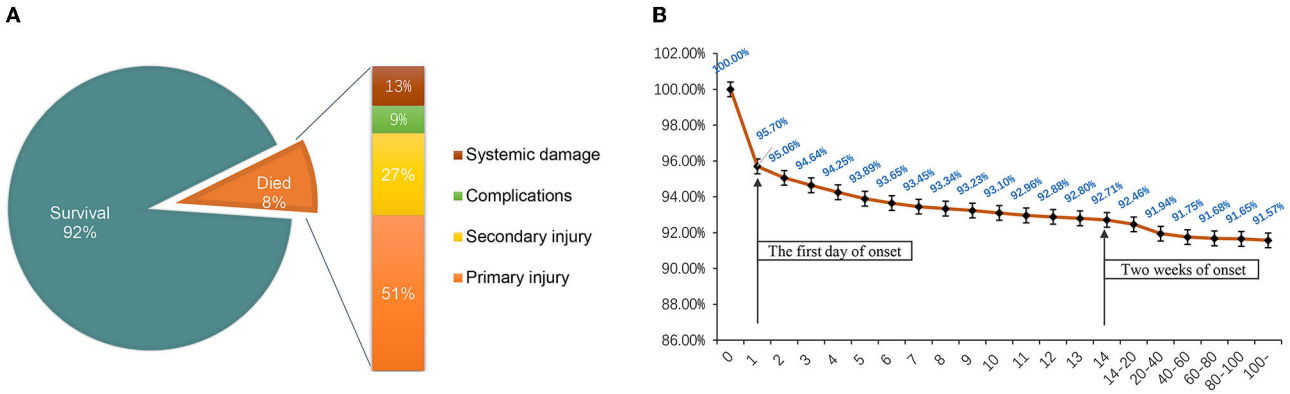

FIGURE 4
(A) Mortality ratio and causes of death of hospitalized patients. **(B)** Survival of hospitalized patients over time. The death peak was on the first day of onset, and most patients died within 2 weeks of hospitalization.

Among the causes of injury, the proportions of RTI and assaults tended to decrease (53.6 to 41.8% and 13.5 to 4.9%, respectively), while the proportions of GLF tended to increase (13.5 to 35.2%) (Figure 3C). Besides, the median length of stay for patients showed a downward trend, from 14 days in 2003 to 8 days in 2020 (Figure 3D). The changes in other characteristics of patients with TBI (gender, surgical method, severity of GCS based on admission, and severity of ISS based on admission) showed a certain trend over time (Supplementary Figure 2).

Furthermore, the first 9 years (2003–2011) and the second 9 years (2012–2020) were divided into two groups. All factors of the patients were analyzed and compared in the two time periods, and the differences in GCS, ISS, injury causes, treatment, and prognosis were found to be statistically significant ($p < 0.05$) (Table 2).

Mortality

A total of 933 (8.43%) patients died during hospitalization; among them, 818 (23.97%) were patients with severe TBI. The causes of death were reviewed, with primary cerebral injury (51.02%, $n = 476$) as the dominant cause, followed by secondary injuries (26.69%, $n = 249$), such as cerebral edema and

TABLE 3 Univariate analysis of predictors for hospital mortality in all 11,068 patients.

		Survival No. (%) ($n = 10,135$)	Deceased No. (%) ($n = 933$)	*P*-value
Sex	Male	7,788 (76.84%)	743 (79.64%)	$P = 0.326$
	Female	2,349 (23.18%)	191 (20.47%)	
Age (years)	Median	42 (IQR 25–56)	48 (IQR 33–60)	$P < 0.001$
Cause of injury	Road traffic injuries	4,344 (42.86%)	577 (61.84%)	$P < 0.001$
	Falls from heights	1,602 (15.81%)	130 (13.93%)	
	Falls from the ground	2,492 (24.59%)	133 (14.26%)	
	Assaults	975 (9.62%)	41 (4.39%)	
	Other	722 (7.12%)	52 (5.57%)	
GCS score at admission	Mild (13–15)	4,485 (44.25%)	21 (2.25%)	$P < 0.001$
	Moderate (9–12)	3,056 (30.15%)	94 (10.08%)	
	Severe (3–8)	2,594 (25.59%)	818 (87.67%)	
ISS score at admission	Mild to moderate (1–8)	2,110 (20.82%)	0 (0.00%)	$P < 0.001$
	Serious (9–15)	3,763 (37.13%)	15 (1.61%)	
	Severe (16–25)	3,303 (32.59%)	154 (16.51%)	
	Critical (25–75)	959 (9.46%)	764 (81.89%)	
Diagnosis	CC	4,915 (48.50%)	557 (59.70%)	$P < 0.001$
	T-SAH	4,368 (43.10%)	476 (51.02%)	
	A-SDH	2,860 (28.22%)	433 (46.41%)	
	SF	1,707 (16.84%)	171 (18.33%)	
	A-EDH	2,182 (21.53%)	165 (17.68%)	
	DAI	282 (2.78%)	71 (7.61%)	
Associated injuries	Chest trauma	1,204 (11.88%)	158 (16.93%)	$P < 0.001$
	Limb injuries	1,891 (18.66%)	287 (30.76%)	
Shock	Shock	684 (6.75%)	330 (35.37%)	$P < 0.001$
	Non-shock	9,451 (93.25%)	603 (64.63%)	
Treatment	Non-surgical	5,170 (51.01%)	257 (27.55%)	$P < 0.001$
	Surgical	4,965 (48.99%)	676 (72.45%)	
Length of stay (d)	ICU length (d)	2 (IQR 0–5)	1 (IQR 1–5)	$P < 0.001$
	ICU length (d)	2 (IQR 0–5)	1 (IQR 1–5)	

GCS, Glasgow Coma Scale; ISS, injury severity score; CC, cerebral contusion; T-SAH, traumatic subarachnoid hemorrhage; A-SDH, acute subdural hematoma; SF, skull fractures (including the base of skull fractures); A-EDH, acute epidural hematoma; DAI, diffuse axial cord injury.

postoperative hypercranial pressure; complications (9.00%, $n = 84$), including intracranial infection and pulmonary infection; and systemic injury (13.29%, $n = 124$), including multiorgan functional deficit (Figure 4A). The survival of patients during hospitalization varied with the length of hospitalization, among which the death of patients on the first day of admission was the most common (Figure 4B). Univariate analysis showed that age, cause of injury, GCS at admission, ISS at admission, shock state at admission, TBI-related diagnoses (CC, T-SAH, A-SDH, SF, and A-EDH), and treatments were significantly associated with mortality (Table 3). Further binary logistic analysis revealed seven potential risk factors for inpatient mortality as follows: sex (female vs. male) (OR, 0.755; 95% CI, 0.62–0.916; $p < 0.005$), GCS (moderate vs. mild) (OR, 1.801; 95% CI, 1.416–2.299; $p < 0.001$), GCS (severe vs. mild) (OR, 2.587; 95% CI, 2.073–3.245; $p < 0.001$), ISS (severe vs. mild) (OR, 1.703; 95% CI, 1.209–2.448; $p < 0.001$), ISS (critical vs. mild) (OR, 18.764; 95% CI, 13.466–20.749; $p < 0.001$), shock (OR 2.103; 95% CI, 1.736–2.547; $p < 0.001$), A-SDH (OR 1.386; 95% CI, 1.173–1.636; $p < 0.001$), and T-SAH (OR 0.807; 95% CI, 0.682–0.953; $p < 0.012$) (Figure 5).

Nomogram

Univariate and binary logistic analyses were performed with the training cohort ($n = 9,949$, 91.30%). In the training cohort, several factors were markedly associated with poor prognosis: age, cause of injury, GCS score at admission, ISS score at admission, CC,

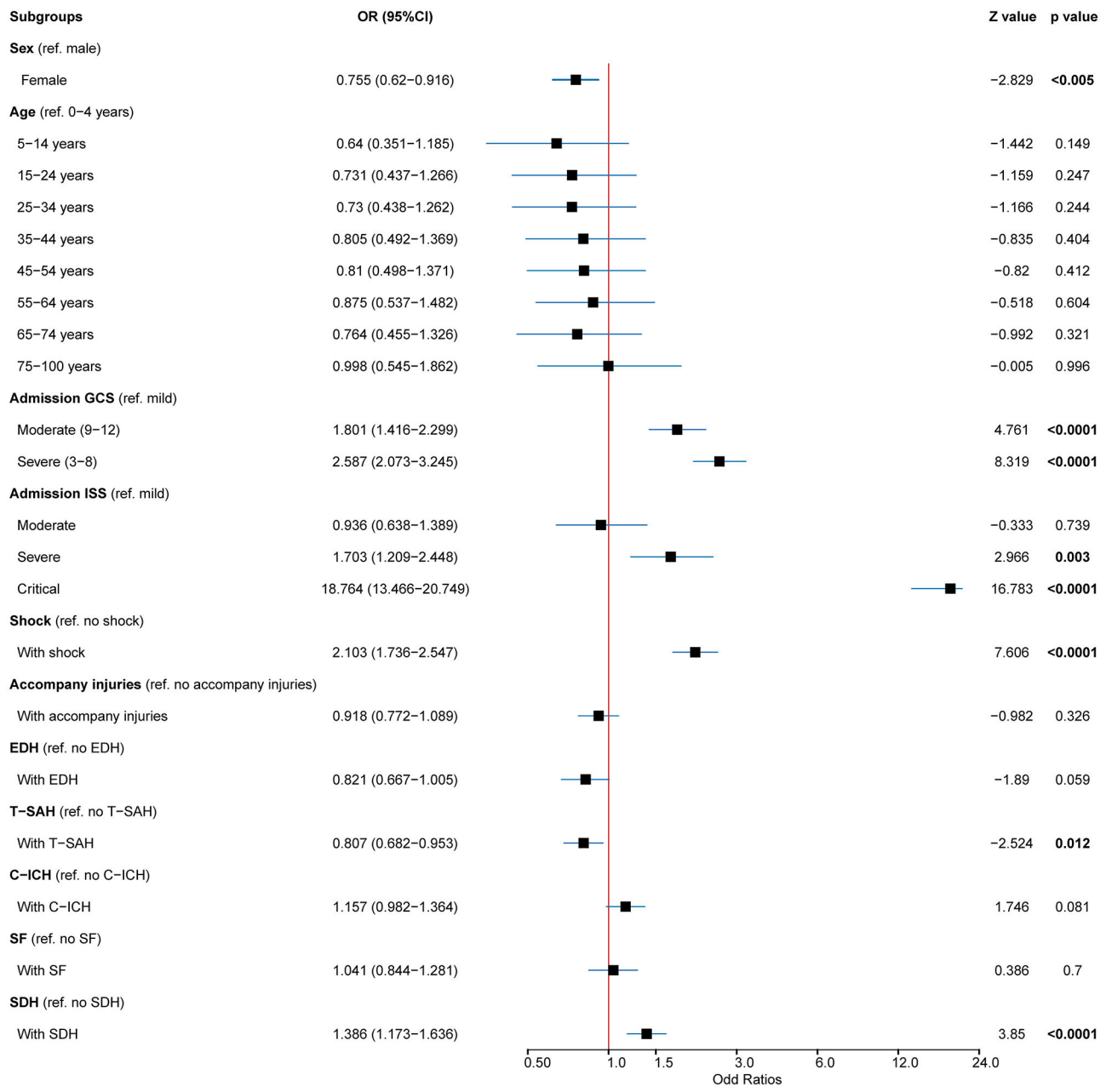

FIGURE 5
Predictors for mortality in patients with TBI. Multivariable analysis in patients with TBI showed that the mortality predictors for cases included age, GCS, ISS, shock, A-SDH, A-EDH, and T-SAH. TBI, traumatic brain injury; GSC, Glasgow Coma Scale; ISS, injury severity score; A-SDH, acute subdural hematoma (A-SDH); A-EDH, acute epidural hematoma; T-SAH, traumatic subarachnoid hemorrhage. Error bars represent 95% CI.

SAH, SDH, SF, EDH, shock, associated injuries, and treatment ($p < 0.001$) (Table 4).

Independent variables were determined by stepwise regression analysis. After excluding the variables with poor prediction performance or multicollinearity, the following eight variables with prognostic significance were obtained: age (45–65 vs. 0–14 years) [$p < 0.001$; OR 1.39 (95% CI: 1.033–1.872)], age (over 65 vs. 0–14 years) [$p < 0.001$; OR 1.919 (95% CI: 1.367–2.696)], GCS (moderate vs. mild) [$p < 0.001$; OR 1.709 (95% CI:1.384–2.11)], GCS (severe vs. mild) [$p < 0.001$; OR 3.256 (95% CI:2.68–3.957)], ISS (serious vs. mild) [$p < 0.04$; OR 1.509 (95% CI: 1.019–2.232)], ISS (severe vs. mild) [$p < 0.04$; OR 6.578 (95% CI: 4.644–9.316)], ISS (critical vs. mild) [$p < 0.001$; OR 145.106 (95% CI: 99.855–210.864)], SDH [$p < 0.001$; OR 1.391 (95% CI: 1.18–1.64)], EDH [$p < 0.008$; OR 0.769 (95% CI:0.633–0.934)], shock [$p < 0.001$; OR 5.897 (95% CI: 4.746–4.746)], accompanying injury [$p < 0.014$; OR 0.805 (95% CI: 0.677–0.956)], and treatment [$p < 0.001$; OR 1.433 (95% CI: 1.207–1.702)] (Table 5).

The established nomogram is presented in Figure 6A. With bootstrapping, internal validation showed that the C-statistic for the risk score was 93.04% (95% CI: 92.3–93.70) (mean absolute error was 0.05) (Figure 6B). The calibration curve analysis of

TABLE 4 Univariate analysis of the training cohort.

		Good prognosis NO. (%)	Poor prognosis NO. (%)	*P*-value	OR (95% CI)
Total		8,086 (81.27)	1,863 (18.73)		
Sex				$P = 0.472$	
	Male	6,222 (81.1)	1,448 (18.9)		
	Female	1,864 (81.8)	415 (18.2)		
Age (years)				$P < 0.001$	
	0–14 years	1,097 (91.5)	102 (8.5)		
	15–44 years	3,627 (84)	693 (16)	$P < 0.001$	2.055 (1.651–2.557)
	45–65 years	2,586 (77.4)	757 (22.6)	$P < 0.001$	3.148 (2.53–3.917)
	Over 65 years	776 (71.4)	311 (28.6)	$P < 0.001$	4.31 (3.384–5.489)
Cause of injury				$P < 0.001$	
	Road traffic injuries	3,569 (79.3)	934 (20.7)		
	Falls from heights	1,244 (79.7)	317 (20.3)	$P = 0.715$	0.974 (0.844–1.123)
	Falls from the ground	1,918 (84.2)	359 (15.8)	$P < 0.001$	0.715 (0.626–0.818)
	Assaults	835 (86.7)	128 (13.3)	$P < 0.001$	0.586 (0.48–0.715)
	Other	520 (80.6)	125 (19.4)	$P = 0.424$	0.919 (0.746–1.131)
GCS score at admission				$P < 0.001$	
	Mild	3,772 (93.1)	281 (6.9)		
	Moderate	2,382 (83.6)	467 (16.4)	$P < 0.001$	2.632 (2.25–3.078)
	Severe	1,932 (63.4)	1,115 (36.6)	$P < 0.001$	7.747 (6.722–8.928)
ISS score at admission				$P < 0.001$	
	Mild (ISS 1–8)	1,902 (98.1)	37 (1.9)		
	Serious (ISS 9–15)	3,409 (97.3)	95 (2.7)	$P = 0.067$	1.433 (0.976–2.103)
	Severe (ISS 16–25)	2,570 (83.2)	518 (16.8)	$P < 0.001$	10.361 (7.384–14.539)
	Critical (ISS 25)	205 (14.5)	1,213 (85.5)	$P < 0.001$	304.17 (212.76–434.85)
CC	Yes	3,761 (77.5)	1,089 (22.5)	$P < 0.001$	1.618 (1.461–1.792)
	No	4,325 (84.8)	774 (15.2)		
SAH	Yes	3,226 (77)	965 (23)	$P < 0.001$	1.619 (1.463–1.791)
	No	4,860 (84.4)	898 (15.6)		
SDH	Yes	1,934 (71.3)	778 (28.7)	$P < 0.001$	2.281 (2.053–2.534)
	No	6,152 (85)	1,085 (15)		
SF	Yes	1,338 (79.1)	354 (20.9)	$P = 0.011$	1.183 (1.039–1.347)
	No	6,748 (81.7)	1,509 (18.3)		
EDH	Yes	2,122 (73)	784 (27)	$P = 0.001$	0.81 (0.712–0.922)
	No	5,964 (84.7)	1,079 (15.3)		
Shock	Yes	279 (30.8)	627 (69.2)	$P < 0.001$	14.195 (12.178–16.546)
	No	7,807 (86.3)	1,236 (13.7)		
Concomitant diagnosis	Yes	2,122 (73)	784 (27)	$P < 0.001$	2.042 (1.84–2.267)
	No	5,964 (84.7)	1,079 (15.3)		
Treatments	Non-surgical	4,612 (90.7)	472 (9.3)	$P < 0.001$	3.912 (3.493–4.382)
	Surgical	3,474 (71.4)	1,391 (28.6)		

GCS, Glasgow Coma Scale; ISS, injury severity score; CC, cerebral contusion; T-SAH, traumatic subarachnoid hemorrhage; A-SDH, acute subdural hematoma; SF, skull fractures (including the base of skull fractures); A-EDH, acute epidural hematoma; DAI, diffuse axial cord injury.

TABLE 5 Multivariate logistic regression analysis on the training cohort.

		P-value	OR (95% CI)
Age (years)		$P < 0.001$	
	0–14 years*	Ref	Ref
	15–44 vs. 0–14 years	$P = 0.538$	1.097 (0.818–1.471)
	45–65 vs. 0–14 years	$P = 0.03$	1.39 (1.033–1.872)
	Over 65vs. 0–14 years	$P < 0.001$	1.919 (1.367–2.696)
GCS score at admission		$P < 0.001$	
	Mild*	Ref	Ref
	Moderate vs. mild	$P < 0.001$	1.709 (1.384–2.11)
	Severe vs. mild	$P < 0.001$	3.256 (2.68–3.957)
ISS score at admission		$P < 0.001$	
	Mild to moderate (ISS 1–8)*	Ref	Ref
	Serious (ISS 9–15) vs. (ISS 1–8)	$P = 0.04$	1.509 (1.019–2.232)
	Severe (ISS 16–25) vs. (ISS 1–8)	$P < 0.001$	6.578 (4.644–9.316)
	Critical (ISS 25) vs. (ISS 1–8)	$P < 0.001$	145.11 (99.86–210.86)
SDH	Yes	$P < 0.001$	1.391 (1.18–1.64)
EDH	Yes	$P = 0.008$	0.769 (0.633–0.934)
Shock	Yes	$P < 0.001$	5.897 (4.746–7.326)
Associated injuries	Yes	$P = 0.014$	0.805 (0.677–0.956)
Treatment	Surgical	$P < 0.001$	1.433 (1.207–1.702)

GCS, Glasgow Coma Scale; ISS, injury severity score; SDH, subdural hematoma; EDH, epidural hematoma; OR, odds ratio; 95% CI 95%, confidence interval. *Control group.

this predictive model exhibited good agreement (slope of 0.8432 and intercept of −0.1108). Across the reasonable threshold probabilities, our nomogram had a higher net benefit than each factor alone (Figure 6C).

External validation was conducted using a validation cohort of 1,119 patients from 2018 to 2020. The prediction model had an accuracy, while the area under the curve (AUC) of the prediction model was 81.02% (95% CI: 80.3–82.70) (Figure 6D). Besides, calibration curve analysis of the prediction model revealed a good agreement in the validation cohort (slope of 0.8358 and intercept of −0.1107; Figure 6E).

Discussion

The absolute number of patients with TBI in China exceeds that of most countries in the world, which has resulted in serious consequences and a huge economic burden. It is a huge challenge to increase the survival rate and cure rates for patients with TBI. Elucidation of the characteristics and changes in incidences of TBI will inform the treatment of TBI in China. In our study, based on 18-year consecutive clinical data in a tertiary hospital in West China, we retrospectively summarized the general characteristics and variation trend of patients with TBI and finally established a nomogram prediction model of poor prognosis to help future treatment and decision-making.

Notably, our current results presented a "dual-feature" on the dynamic shifting of injury patterns and affected populations in patients with TBI. In our current cohort, the patients with TBI were predominantly male (aged between 25 and 56 years), and RTI was the leading cause of death. Meanwhile, the incidence of RTI and assaults decreased over time, while the incidence of TBI increased in the GLF group. These results might be attributed to extensive social involvement and high exposure risks among middle- and young-aged men, especially with the fast-growing public transportation infrastructure and socioeconomic activities in the past decades. Evidence suggested varied injury patterns across different income countries: patients with TBI in middle-income and low-income countries were generally younger, vulnerable road-traffic users, and increased motorization, inadequate traffic education, and delayed traffic safety regulation implementation were the main causes for the TBI in these countries (15–17). In terms of high-income country counterparts, who were generally motor-vehicle occupants, studies witnessed an epidemiological shift toward an elderly population affected by TBI, who were predominantly advanced in age (>50 years) and resulting in more fallen associated contusion injuries (18–21).

Considering the rapid urbanization, improved traffic regulation, and aging population in the past decades in China, it was not surprising that our results simultaneously reflected both the characteristics of middle- and low-income countries and high-income countries. First, preventive measures improved traffic safety and reduced the incidence of traffic accidents, which especially decreased the risk for younger individuals (5, 22). Second, the implementation of the amended Criminal Law, which imposed harsher punishments on driving under the influence

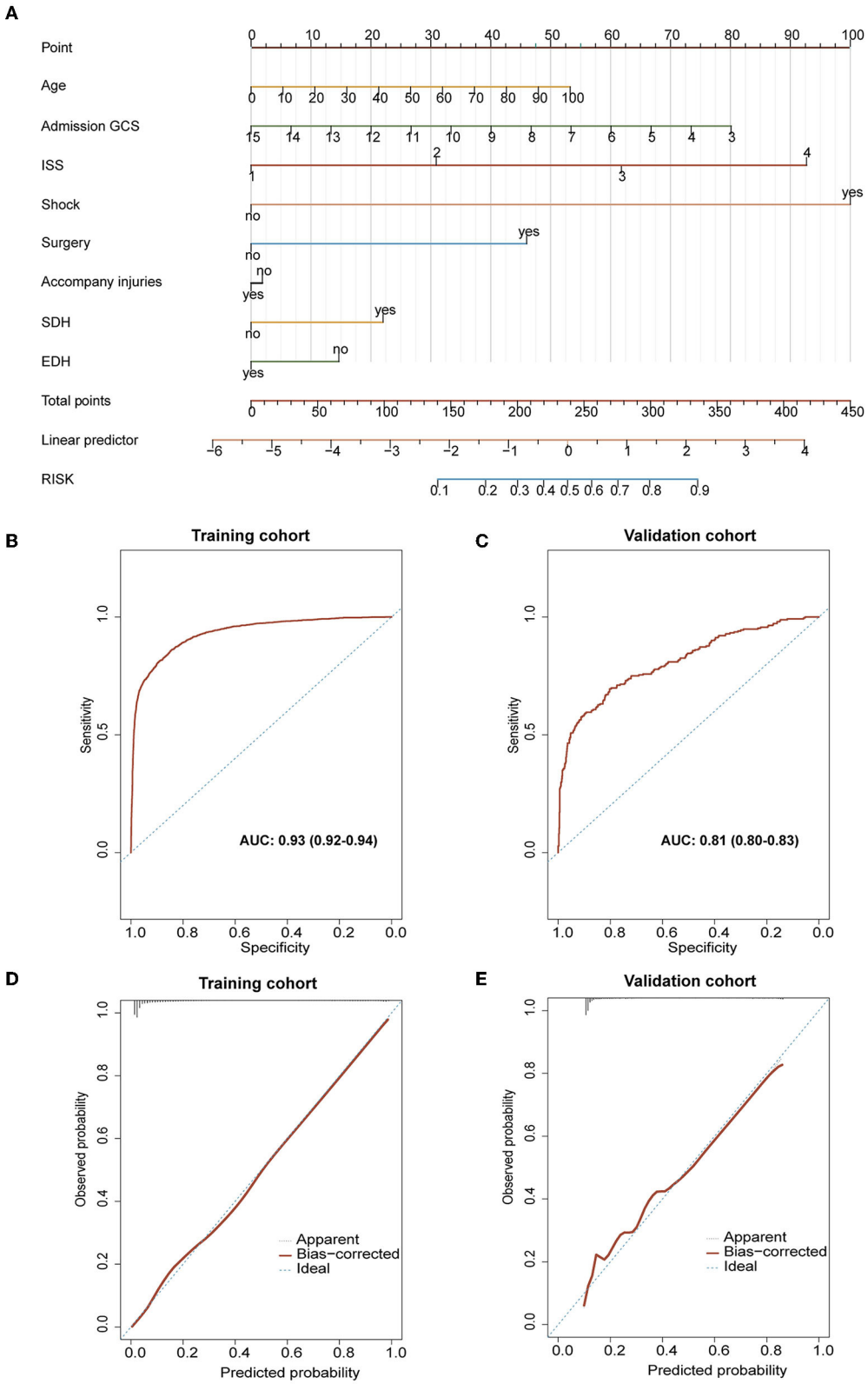

FIGURE 6
Evaluation of related characteristics as prognostic indicators for the prognosis of TBI. **(A)** The prediction model of poor prognosis was established and expressed by nomogram. **(B, C)** The results of calibration and ROC curve analysis of the purposed nomogram. **(B)** The AUC of the purposed nomogram for predicting poor prognosis in the training cohort was 93.04% (95% CI: 92.3–93.70). **(C)** The calibration curve analysis of the nomogram in the training cohort. The dashed line stands for perfect prediction. The dotted line represents apparent estimates of predicted vs. observed values, meanwhile, the solid line (on behalf of bias) shows the corrected estimates *via* employing 1,000 bootstrap samples. ROC, receiver operating

(Continued)

FIGURE 6 (Continued)
characteristic curve; AUC, the area under the ROC curve. **(D, E)** The results of calibration and ROC curve analysis of the purposed nomogram for predicting poor prognosis occurrence in the external validation cohort. **(D)** The AUC of the purposed nomogram for predicting poor prognosis in the validation cohort was 81.02% (95% CI: 80.3–82.70). **(E)** The calibration curve analysis of the nomogram in the validation cohort. The dashed line stands for perfect prediction. The dotted line represents apparent estimates of predicted vs. observed values, and the solid line (on behalf of bias) shows the corrected estimates *via* employing 1,000 bootstrap samples.

(DUI), demonstrated unequivocal success, and the incidence of traffic accident-related TBI has decreased by over 50% since 2011 (9). Our results also confirmed this positive phenomenon. In addition, increased life expectancy and greater mobility for the elderly population were the main contributors to the rise in the absolute incidence of TBI among the elderly (23, 24). Therefore, this shifting paradigm may highlight both the pace of rapid urbanization and aging in developing countries, especially China, which will be of great help to future public health and policymaking for the approaches of prevention, management, and post-injury care for patients with TBI.

The in-hospital mortality rate in our study was 9.33%. Previously, Wu et al. (25) reported a mortality rate of 10.8%, while Gao et al. (9) reported a rate of 5%. Discrepancies in these in-hospital mortality rates among studies implied varied accessibility of medical systems, treatment strategies, and imbalanced regional development. We found a significantly high mortality rate among patients with low GCS scores, low ISS scores, and a combined shock state on admission, indicating that excess primary injury to the brain was the primary cause of death. Therefore, early diagnosis and treatment were the key to manage severe TBI. Active interventions should be made to prevent further exacerbations of TBI.

Since 2011, the inpatient mortality rate has decreased with the introduction of ICP in our institution. Chiara et al. reported that the 6-month mortality rate was low in patients on ICP [441/1,318 (34%)], compared to patients without ICP [517/1,049 (49%); $p < 0.0001$] (26). ICP monitoring could timely detect ICP changes, rapidly demonstrate the effect sizes of surgical treatments, and indicate the necessity for further interventions in the early stages (26–30). Our results reiterated that the application of ICP was a pivotal factor in improving the prognosis of patients with TBI.

Clinical diagnosis and treatment decision models for craniocerebral injuries are vital for improving clinical outcomes for critically ill patients in the emergency and ICU departments. Currently, the two most influential prognostic models for TBI are the International Collaboration for Prognostic Clinical Testing and Research in Craniocerebral Injury (IMPACT) and the Collaboration for Randomized Studies after Craniocerebral Injury (CRASH). Our nomogram, which incorporated eight factors (age, GCS, ISS, SDH, EDH, shock, accompanying injury, and treatment), demonstrated good discrimination and calibration abilities. Compared to CRASH, our prediction model had several comparable factors, while the ISS was unique and could not be ignored based on our data. The GCS and ISS scores and shock were the leading factors and were measured by the standard deviation of the nomogram. GCS was the most important predictor of total mortality in patients with TBI, and GCS ≤ 8 for TBI was considered severe (31).

However, for patients with multiple injuries, combined injuries, and complex injuries, prognosis or mortality usually could not be rapidly assessed by GCS alone. The ISS was potentially a good predictor of death in trauma patients (32). A Japanese study focusing on prognostic factors for TBI found that ISS and injury mechanisms were strongly associated with mortality outcomes (4). Considering the multiple factors associated with TBI, including medical and socioeconomic elements, we proposed a more comprehensive model to reflect the dynamic changes during TBI treatment. In recent years, many nomogram models for TBI have been developed for prognostic prediction based on clinicopathological factors (12, 33). For example, a multicenter observational study proposed an algorithm based on nomograms that can predict mortality in real-time during intensive care after TBI (34). The nomogram prediction model that we established integrated the factors involved in TBI prognosis with more inclusive and specific elements, reflecting temporal shifts in TBI therapeutic approaches and regimes (35).

In the analysis of mortality and prognostic factors, it is noteworthy that patients with EDH seem to have a better prognosis. Comparative analysis based on our study found that patients in the EDH group were younger than those in the non-EDH group (5 vs. 13.7%), had a lower incidence of shock at admission (6.90 vs. 9.80%), and had a higher rate of surgery (64.60 vs. 47.30%). There have been some consistent reports in previous studies. Taussky et al. (36) observed that the mortality rate of SDH was 41% (19/46), while the mortality rate of patients with EDH was 3% (1/37). Therefore, patients with EDH in TBI seem to have a better prognosis.

Limitations

As a single-center retrospective study spanning decades, data from patients' long-term follow-up were unretrievable for certain cases. In addition, with changes in treatment modalities over 18 years, data heterogeneity was inevitable, resulting in the inability to further certain stratifications. Regarding the establishment of the prediction model, our results were relatively optimistic. However, external data for consistency and calibration evaluation were warranted.

Conclusion

Most of the patients with TBI were middle-aged men, and RTI was the leading cause of death. Low GSC score, high ISS score, or concomitant shock state at admission were independent risk factors for TBI. The incidence of TBI was increasing in people over 45 years of age. The incidence of RTI and assaults declined over time, while the incidence of GLF increased. Finally, we proposed a nomogram for poor prognosis and validated its

efficacy with good reliability, which may help in the exploration and research of future prevention and treatment of TBI. Our findings demonstrated the demographic characteristic changes and regime shifts of patients with TBI in a large city in western China and may provide experience for the future treatment of TBI, especially in developing countries with a rapid process of urbanization.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Research Board of Tangdu Hospital, Fourth Military Medical University (TDLL-202207-08). Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

SGu had full access to the entire data in the study and took responsibility for the integrity and accuracy of the data analysis. Concept and design: PJ, YW, LW, and YQ. Acquisition and analysis or interpretation of data: SGu, RH, FC, PJ, JL, YZ, MC, WZ, YJ, SGe, YW, LW, and YQ. Drafting of the manuscript: SGu, RH, FC, CF, and YJ. Critical revision of the manuscript for important intellectual content: SGu, RH, FC, YW, and LW. Statistical analysis: SGu, RH, FC, PJ, JL, YZ, MC, WZ, TH, and NW. Obtained funding: YW, LW, and YQ. Administrative, technical, or material support: SGu, RH, FC, SGe, JL, YZ, MC, WZ, TH, NW, and YJ. Supervision: TH, SGe, YW, LW, and YQ. All authors reviewed the manuscript, contributed to the article, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1138217/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Some of the other features of brain injury. **(A)** The most common causes of different degrees of brain damage vary. Assault (59.35%) is the most common cause of mild brain injury, and traffic accident (36.96%) is the most common cause of severe brain injury. **(B–D)** The onset time of patients with TBI showed certain regularity in the month, week, and day. **(B)** TBI occurred most in September (1,034 cases, 9.34%) and least in February (735 cases, 6.64%). **(C)** The incidence rate was the highest on Saturday and Sunday (14.76% and 14.57%). **(D)** The peak time point was 17:00 [$n = 781$ (8.1%)] every day. 05:00–06:00 is the low time point.

SUPPLEMENTARY FIGURE 2
From 2003 to 2020, the general characteristics of patients with TBI showed a certain trend over time. **(A, B)** Gender and treatment change over time. **(C, D)** TBI severity (GCS and ISS) changes over time.

SUPPLEMENTARY TABLE 1
Univariate analysis of training cohort and validation cohort.

References

1. Brazinova A, Rehorcikova V, Taylor MS, Buckova V, Majdan M, Psota M, et al. Epidemiology of traumatic brain injury in europe: a living systematic review. *J Neurotraum.* (2021) 38:1411–40. doi: 10.1089/neu.2015.4126

2. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol.* (2017) 16:987–1048. doi: 10.1016/S1474-4422(17)30371-X

3. Steyerberg EW, Wiegers E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: A European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol.* (2019) 18:923–34. doi: 10.1016/S1474-4422(19)30232-7

4. Maeda Y, Ichikawa R, Misawa J, Shibuya A, Hishiki T, Maeda T, et al. External validation of the TRISS, CRASH, and IMPACT prognostic models in severe traumatic brain injury in Japan. *PLoS ONE.* (2019) 14:e221791. doi: 10.1371/journal.pone.0221791

5. Jiang J, Gao G, Feng J, Mao Q, Chen L, Yang X, et al. Traumatic brain injury in China. *Lancet Neurol.* (2019) 18:286–95. doi: 10.1016/S1474-4422(18)30469-1

6. Cheng P, Yin P, Ning P, Wang L, Cheng X, Liu Y, et al. Trends in traumatic brain injury mortality in China, 2006–2013: a population-based longitudinal study. *PLoS Med.* (2017) 14:e1002332. doi: 10.1371/journal.pmed.1002332

7. Yang C, Lang L, He Z, Hui J, Jiang J, Gao G, et al. Epidemiological characteristics of older patients with traumatic brain injury in china. *J Neurotraum.* (2022) 39:850–9. doi: 10.1089/neu.2021.0275

8. Zheng X, Yi Q, Xu X, Meng R, Ma S, Tang S, et al. Trends and external causes of traumatic brain injury and spinal cord injury mortality in south China, 2014–2018: an ecological study. *BMC Public Health*. (2021) 21:2225. doi: 10.1186/s12889-021-12225-2

9. Gao G, Wu X, Feng J, Hui J, Mao Q, Lecky F, et al. Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective,

multicentre, longitudinal, observational study. *Lancet Neurol.* (2020) 19:670–7. doi: 10.1016/S1474-4422(20)30182-4

10. Jiang J. Head trauma in China. *Injury.* (2013) 44:1453–7. doi: 10.1016/j.injury.2012.08.045

11. van Dijck JTJM, Bartels RHMA, Lavrijsen JCM, Ribbers GM, Kompanje EJO, Peul WC. The patient with severe traumatic brain injury. *Curr Opin Crit Care.* (2019) 25:622–9. doi: 10.1097/MCC.0000000000000671

12. Sheng J, Chen W, Zhuang D, Li T, Yang J, Cai S, et al. A clinical predictive nomogram for traumatic brain parenchyma hematoma progression. *Neurol Ther.* (2022) 11:185–203. doi: 10.1007/s40120-021-00306-8

13. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. a practical scale. *Lancet.* (1974) 2:81. doi: 10.1016/S0140-6736(74)91639-0

14. Baker SP, O'Neill B, Haddon WJ, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma.* (1974) 14:187–96. doi: 10.1097/00005373-197403000-00001

15. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung Y, Punchak M, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg.* (2019) 130:1080–97. doi: 10.3171/2017.10.JNS17352

16. Abio A, Bovet P, Valentin B, Bärnighausen T, Shaikh MA, Posti JP, et al. Changes in mortality related to traumatic brain injuries in the seychelles from 1989 to 2018. *Front Neurol.* (2021) 12:720434. doi: 10.3389/fneur.2021.720434

17. Maas AIM, Stocchetti NM, Bullock RM. Moderate and severe traumatic brain injury in adults. *Lancet Neurol.* (2008) 7:728–41. doi: 10.1016/S1474-4422(08)70164-9

18. Khan UR, Razzak JA, Wärnberg MG. Global trends in adolescents' road traffic injury mortality, 1990–2019. *Arch Dis Child.* (2021) 106:753–7. doi: 10.1136/archdischild-2020-319184

19. Feigin VL, Theadom A, Barker-Collo S, Starkey NJ, McPherson K, Kahan M, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *Lancet Neurol.* (2013) 12:53–64. doi: 10.1016/S1474-4422(12)70262-4

20. Cole TB. Global road safety crisis remedy sought. *JAMA.* (2004) 291:25–31. doi: 10.1001/jama.291.1.31

21. Roozenbeek B, Maas AIR, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol.* (2013) 9:231–6. doi: 10.1038/nrneurol.2013.22

22. Lieutaud T, Gadegbeku B, Ndiaye A, Chiron M, Viallon V. The decrease in traumatic brain injury epidemics deriving from road traffic collision following strengthened legislative measures in France. *PLoS ONE.* (2016) 11:e167082. doi: 10.1371/journal.pone.0167082

23. Sarmiento K, Thomas K, Daugherty J, Haarbauer-Krupa J, Waltzman D. State-Level numbers and rates of traumatic brain Injury-Related emergency department visits, hospitalizations, and deaths by age, 2014. *J Head Trauma Rehab.* (2020) 35:E469–80. doi: 10.1097/HTR.0000000000000594

24. Sun D, Jiang B, Ru X, Sun H, Fu J, Wu S, et al. Prevalence and altered causes of traumatic brain injury in china: a nationwide survey in 2013. *Neuroepidemiology.* (2020) 54:106–13. doi: 10.1159/000501911

25. Wu X, Hu J, Zhuo L, Fu C, Hui G, Wang Y, et al. Epidemiology of traumatic brain injury in eastern china, 2004: a prospective large case study. *J Trauma.* (2008) 64:1313–9. doi: 10.1097/TA.0b013e318165c803

26. Robba C, Graziano F, Rebora P, Elli F, Giussani C, Oddo M, et al. Intracranial pressure monitoring in patients with acute brain injury in the intensive care unit (SYNAPSE-ICU): an international, prospective observational cohort study. *Lancet Neurol.* (2021) 20:548–58. doi: 10.1016/S1474-4422(21)00138-1

27. Chesnut R, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, et al. A management algorithm for adult patients with both brain oxygen and intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intens Care Med.* (2020) 46:919–29. doi: 10.1007/s00134-019-05900-x

28. Harary M, Dolmans RG, Gormley W. Intracranial pressure monitoring—review and avenues for development. *Sensors.* (2018) 18:465. doi: 10.3390/s18020465

29. Changa AR, Czeisler BM, Lord AS. Management of elevated intracranial pressure: a review. *Curr Neurol Neurosci.* (2019) 19:99. doi: 10.1007/s11910-019-1010-3

30. Feng J, Yang C, Jiang J. Real-world appraisal of intracranial pressure monitoring. *Lancet Neurol.* (2021) 20:502–3. doi: 10.1016/S1474-4422(21)00164-2

31. Huang J, Tsai Y, Rau C, Hsu S, Chien P, Hsieh H, et al. Systolic blood pressure lower than the heart rate indicates a poor outcome in patients with severe isolated traumatic brain injury: a cross-sectional study. *Int J Surg.* (2019) 61:48–52. doi: 10.1016/j.ijsu.2018.11.030

32. Majdan M, Brazinova A, Rusnak M, Leitgeb J. Outcome prediction after traumatic brain injury: comparison of the performance of routinely used severity scores and multivariable prognostic models. *J Neurosci Rural Pract.* (2019) 08:20–9. doi: 10.4103/0976-3147.193543

33. Zheng R, Zhao Z, Yang X, Jiang S, Li Y, Li W, et al. Initial CT-based radiomics nomogram for predicting in-hospital mortality in patients with traumatic brain injury: a multicenter development and validation study. *Neurol Sci.* (2022) 43:4363–72. doi: 10.1007/s10072-022-05954-8

34. Najafi Z, Zakeri H, Mirhaghi A. The accuracy of acuity scoring tools to predict 24-h mortality in traumatic brain injury patients: a guide to triage criteria. *Int Emerg Nurs.* (2018) 36:27–33. doi: 10.1016/j.ienj.2017.08.003

35. Hukkelhoven CWPM Eijkemans MJC, Steyerberg EW. Predicting survival using simple clinical variables: a case study in traumatic brain injury. *J Neurol Neurosurg Psychiatry.* (2000) 68:396–7. doi: 10.1136/jnnp.68.3.396a

36. Taussky P, Widmer HR, Takala J, Fandino J. Outcome after acute traumatic subdural and epidural haematoma in Switzerland: a single-centre experience. *Swiss Med Wkly.* (2008) 138:281–5. doi: 10.4414/smw.2008.12056

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Models of traumatic brain injury-highlights and drawbacks

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Traumatic brain injury (TBI) is the leading cause for high morbidity and mortality rates in young adults, survivors may suffer from long-term physical, cognitive, and/or psychological disorders. Establishing better models of TBI would further our understanding of the pathophysiology of TBI and develop new potential treatments. A multitude of animal TBI models have been used to replicate the various aspects of human TBI. Although numerous experimental neuroprotective strategies were identified to be effective in animal models, a majority of strategies have failed in phase II or phase III clinical trials. This failure in clinical translation highlights the necessity of revisiting the current status of animal models of TBI and therapeutic strategies. In this review, we elucidate approaches for the generation of animal models and cell models of TBI and summarize their strengths and limitations with the aim of exploring clinically meaningful neuroprotective strategies.

KEYWORDS

traumatic brain injury, animal models, cell models, neuroprotective strategies, advantages and disadvantages

1. Introduction

TBI is a serious problem worldwide. Approximately 10 million people worldwide suffer TBI each year, and a significant number of patients die as a result, or become temporarily or permanently disabled (1, 2). For example, in 2013, there were 2.5 million emergency hospital visits, 280,000 hospitalizations, and 56,000 deaths from TBI in the United States (3); 2.1 million patients, in Europe, were admitted to hospital due to TBI, 82,000 died (4). It was estimated that the death rate of TBI in China was about 13 cases per 100,000 people, similar to reported death rates in other countries (5). In addition, TBI has been confirmed to be closely associated with epilepsy, Alzheimer's disease, Parkinson's disease, chronic neuroinflammation and other diseases (2, 6–10). In order to find a rational treatment plan for TBI, a large number of *in vitro*, cellular and *in vivo*, animal models have been established to study the pathogenesis of TBI. Different animal models have been established to replicate different types of TBI. Although larger animals are more similar to humans in size and physiology, rodents have been widely used in TBI models because of their small size, low cost and easy quantification (10, 11). Early TBI models mainly simulated the biomechanical changes of brain injury, while the models created in recent years have been used to study molecular mechanisms and molecular cascades triggered by head trauma (11–13). *In vitro* TBI models are also potentially important tools to study its pathophysiology. Compared with *in vivo* models, *in vitro* models have the advantages of good repeatability, good controllability, lower experimental costs and fewer ethical problems. Therefore *in vitro* models allow us for large scale production, enabling for reliable and efficient drug screening. Common TBI models can be divided, according to the different modes of injury,

into mechanical injury, pressure injury, explosion injury and repetitive minor injury models. In this paper, we review, the above commonly used models, aimed at discovery of effective clinical neuroprotective treatments.

2. Mechanical force injury models

2.1. Mechanical force-induced TBI animal models

Mechanical force-induced TBI animal models commonly involve weight-drop (WD) and controlled cortical impact (CCI) models.

WD is a commonly used method causing brain damage by impact to the dura mater or skull with falling freely weights. A catheter is used to guide freely falling weights with damage controlled by the weight and height of fall (11, 13–15). The Feeney WD model involves mild, moderate and severe brain injury, simulating concussion and brain contusion, by direct impact to the dura mater causing cerebral cortical injury, with adjustment of the weight hitting the head and the height of free fall (16–21). However, craniotomy can lead to cortical contusion, hemorrhagic lesions, blood-brain barrier damage, immune cell infiltration, and glial cell activation, and prolong modeling time. Shapira Y and Flierl MA et al. (22,23) introduced the closed head WD rodent model by fixing the head on a hard platform to avoid the impact of accelerated diffusion damage on rats and mice later. Weight falls on the unprotected skull to replicate mixed focal/diffuse injury. Due to its simple installation, low cost, and the absence of craniotomy surgery, each modeling time can be controlled within 1 min without any other damage caused by craniotomy surgery, so it has been widely used. However, its drawbacks are the poor accuracy and repeatability of the injury site and the higher mortality rate.

The Marmarou WD model makes two improvements on the Feeney model: (1) Anesthetized rats were fixed to a sponge platform, ensuring instantaneous external force, but avoiding a second impact by pulling out the sponge platform after the blow. (2) A metal sheet with a diameter of 1 cm and a thickness of 0.3 cm is placed to ensure the dispersion of external force, simulating diffuse brain injury. The advantages of this model are simplicity and easy to control conditions. Its disadvantage is a higher fatality rate. Marmarou WD mainly replicates diffuse axonal injury caused by external violence injury such as high altitude fall injury and traffic accident, and Marmarou WD causes extensive and bilateral damage to neurons, axons, dendrites and microvessels, especially in the corpus callosum, internal capsule, optic nerve bundle and other parts. It may also lead to motor and cognitive deficits, such as difficulty walking and memory, which are related to the severity of the injury (10, 14, 15, 21, 24).

In the CCI model, impact force is generated by high-speed moving air driving metal to hit the exposed dura mater directly, causing a degree of brain damage. The CCI WD model is mainly used to replicate clinical situations such as cortical tissue loss, acute subdural hematoma, axonal injury, brain concussion, blood–brain barrier dysfunction and even coma after TBI. The investigators performed a comprehensive neuropathological assessment of TBI models of CCI, indicating that the associated brain injuries may be quite extensive, including acute cortical injury, hippocampal and thalamic degeneration, neuronal loss, vascular rupture, edema, and macrophage accumulation. The degree of injury was controlled by adjusting the duration, speed, and depth of the impact (24–27). Researchers used immature pigs to establish CCI WD models to mimic TBI damage in human children (28). The reason why piglets were chosen is that, unlike other animals, pig brain growth peaks around birth and changes in myelination and water content during development are similar to those in human brain development. After CCI, 1-month-old piglets exhibited focal pathophysiology, replicating the TBI reactions observed in preschool and early childhood, where brain swelling was the most prominent. The CCI model of piglets has also been used to identify relevant TBI biomarkers in peripheral blood and to experiment with intervention therapies that have been proposed for clinical translation. Compared with the Shohami, Feeney, Shapira and Marmarou WD models, the CCI model improved mechanical factors and significantly reduced the fatality rate. A brain stereo locator can also be used to accurately locate craniocerebral strike, with more accurate force. In addition, after impact, the impact head can be automatically and rapidly removed to avoid damage due to extrusion or secondary damage due to rebound (12, 26, 27). In conclusion, the CCI model is more accurate, reproducible and stable, assisting the study of TBI biomechanics.

2.2. Mechanical force-induced TBI cellular models

TBI cellular models involve mechanical transection and cell stretch injury. *In vitro* models of mechanical transection, use nerve cell protrusion on the petri dish separated from the cell body by a fine plastic needle, blade or laser, simulating a puncture wound, a penetrating skull fracture or various brain tissue lesions after TBI. Faden et al. (29) used an impact device with 28 stainless steel blades to induce mechanical damage on cultured rat cortical neuron cells. The cutting device produced uniform incisions in the cell layer of the 96-well tissue culture plate with a spacing of 1.2 mm. After 24 h, cell viability was measured by release of lactate dehydrogenase (LDH). The results showed that the cutting device directly caused cell death under the leaf, and within 24 h, the nerve cells around the wound gradually died. Cengiz et al. (30) cultured adult mouse dorsal root ganglion neurons and transected their elongated nerve fibers with a precise laser beam. The cell preparation was observed continuously with time-lapse microscope for 24 h. The more distal the incisions, the longer the degradation field, and thicker axons degraded faster than thinner axons. The advantage of this model was that the position of cutting and the degree of damage were controlled precisely. The model was then simplified by mechanical cutting of cultured rat cortical neurons using a simpler 200 µl yellow spear (diameter 1.5 mm) (31). This method can be used to establish TBI damage of different degrees according to different scratch areas. This simple model requires no special equipment and is easy to operate and effective. However, there is no strict standard for mechanical damage parameters, and damage is only graded by a number of damaged cells. In cellular models of stretch injury, different degrees of stretch caused altered cell morphology, to study biomechanical effects of TBI. widely used model employs compressed gas to deform a clamped circular plate, deforming attached nerve cells, resulting in mild, moderate or severe damage according to the different pressure (32–34). The disadvantages of this model include: uneven deformation at a high deformation rate, and the necessity to verify

cellular adhesion to the substrate. Another widely used model involves a microfluidic device applying gas pressure to a pneumatic channel below a flexible polydimethylsiloxane (PDMS) film, which deforms causing axon tensile damage (35). The advantage of a microfluidic device model is that specific areas of nerve cells (such as cell body or axon) can be specifically damaged. However, its disadvantage is that bulky pneumatic devices are needed, and the equipment and instruments are complicated (36). Currently, stretch injury is considered the gold standard for simulating subfatal traumatic neuronal injury. Its advantages include standardized and reproducible damage, as well as direct, real-time measurement of all biomechanical aspects. It is the most widely used *in vitro* TBI model (37–39).

3. Pressure injury TBI models

TBI animal models of pressure injury largely include Fluid percussion injury (FPI) and Penetrating encephaliclide-like brain injury (PBBI). FPI causes brain tissue deformation and displacement through rapid injection of a certain amount of normal saline into the cranial cavity, resulting in brain injury. The severity of the resulting injury depends on the intensity of the pressure pulse. FPI can replicate human pathophysiological features such as intracranial hemorrhage, brain swelling and progressive gray matter damage after TBI. It is mainly used to replicate clinical TBI without skull fracture (40–46). The FPI model can be divided into central (sutures above sagittal), parsagittal (distance from midline <3.5 mm) and lateral (from the center line >3.5 mm; LFPI) model depending on the location of skull penetration. Early FPI models largely controlled damage severity by controlling the single variable of height of pendulum fall. In order to improve repeatability, Kabadi et al. (47) developed a microprocessor controlled pneumatic device enabling precise control of impact pressure and residence time to reduce the differences between tests. Cognitive dysfunction and neurobehavioral disorders generated by LFPI models are common clinical symptoms in TBI patients. However, due to brain stem damage and prolonged apnea, FPI models have a higher mortality rate than other models. The selection of craniotomy site in rat LFPI models is very important to the degree of injury. Therefore, the location of craniotomy should be precisely controlled to improve the reliability and repeatability of the model. The PBBI model simulates increased intracranial pressure with impact by a high-powered probe with a shock wave that creates a temporary chamber in the brain many times the size of the projectile itself. The degree of damage depends on the ejection path and the energy transferred. Several new PBBI rodent models have been developed. Davis et al. (48) projected the PBBI probe into the right hemisphere of the brain, through the bone window, to a depth of 1.2 cm. The elastic head of the probe was rapidly filled with water and expanded using a computer program, resulting in an oval balloon with a volume equal to 10% of the brain volume. These PBBI models caused white and gray matter injury, brain edema, epilepsy, cortical diffusion, glial cell proliferation, neuroinflammation and so on. and resulting sensory impairment and cognitive dysfunction. Compared with other TBI models, PBBI can cause extensive intracerebral hemorrhage in the entire primary lesion due to injury and the temporary lumen formed (49). PBBI model are the mechanisms of moderate to severe craniocerebral injury.

Pressure injury models include Compression and Vacuum assisted injury models. The pressure injury model in nerve cells replicates the closed brain injury or FPI model by applying pressure to cultured cells to cause damage. However, in order to get a cellular response, pressure must be increased far beyond the levels that occur during TBI. Under these hydrostatic pressure conditions, brain deformation is likely to be minor because brain tissue is almost incompressible and therefore much higher pressures (around 15 atmospheres) are required to cause damage. The researchers cultured nerve cells, connected to a sealed pressurizer, injecting a nitrogen and oxygen mixture, to give different levels of pressure. Cell volume increased after pressure, with edema became more obvious the higher the pressure. The pressure injury model simulates the clinical pathophysiology after TBI, and the method is simple, the conditions are easy to control, with the degree of injury titrated by adjusting the pressure value. It can be applied to the study of mechanical damage to nerve cells in the CNS, as well as to the study of secondary damage after TBI (50, 51). Negative pressure drainage nerve cell models damage axons by using microfluidic devices and laboratory vacuum. Once axonal growth reaches an adjacent compartment, brief vacuuming of the second compartment with a Pasteur suction tube by creates a bubble, shearing only the axon in the second compartment, causing axon damage without affecting the cell body, which can then be used to screen potential treatments for axon regeneration. Microfluidics and vacuum based damage mechanisms can also be used to simulate and characterize acute axonal degeneration (AAD) (36). Zhou et al. (52) used a microfluidic vacuum inhalation injury model to examine the pathway leading to the observed reduced regeneration of mature axons after injury. In mature axons, the anabolic enzyme (SNPH) -mediated mitochondrial anchoring hinders mitochondrial transport, resulting in energy defects at the damaged site. Enhanced mitochondrial transport by deletion of the SNPH gene promotes axon regeneration after injury by increasing mitochondrial transport and maintaining ATP supply to damaged axons. Therefore, the vacuum inhalation injury model can characterize mitochondrial transport and energy supply of damaged axons, providing a new therapeutic strategy for axon regeneration (36). The disadvantage of the vacuum suction method is the high fluid resistance required between interconnected compartments to limit damage to specific neuronal areas. This resistance is usually provided by a microgroove in the microfluidic device allowing the duration and strength of the vacuum to be carefully adjusted to minimize damage to non-specific areas.

4. Blast-induced injury (BTBI) models

Craniocerebral blast injury is mainly caused by blast wave and projectiles; the main type of injury in modern warfare. Domestic and foreign scholars have established various models of BTBI. Among the most common are the free field explosion model, the Blast tube model, the small explosion source model, and the Advanced Blast Simulator; (ABS) (53–56). The ABS model does not use explosives, but rather compressed gas as power. A cylindrical tube is divided into two chambers; the pressurized and the test areas by a thin film of special material. When the pressure in the pressurized area rises to a certain extent, the diaphragm is broken and a shockwave is generated, causing damage to the animal's head, placed in the test area. Uylissa A. Rodriguez et al. (56) adopted a shock tube test area of 2 m

containing the rat's head, with a compression area 2.54 m in length and a diaphragm thickness of 0.4 mm. An animal model of BTBI was established by pressurizing air to about 1,230 kPA to break the diaphragm causing a shock wave, resulting in head injury in the rat. Blast waves can damage cerebral blood vessels, neurons, glial cells and blood–brain barrier, leading to the activation of microglia and neuroinflammatory response (57, 58). Like other injury models, bTBI also exhibits pathological results such as ventricular enlargement, gray/white matter atrophy, axonal injury, cell apoptosis, and neuroinflammation (58, 59). The mechanism of brain damage caused by shock waves is currently unclear.

In the same way, cultured nerve cells and brain tissue sections were placed in the test area of the shock tube to establish a BTBI model *in vitro*. Campos-Pires et al. (60) oriented the cells of the mouse hippocampal brain slice toward the shock tube, and established a trauma model with different impact pressures. The degree of damage degree increased with the increase in impact pressure peak and shock wave. The main mode of cell death induced by the shock wave was apoptosis. Researchers found that after cells were damaged by shock waves, the levels of adenosine triphosphate (ATP) decreased, while LDH and reactive oxygen species were upregulated (61, 62). Ravin et al. (63) used a pneumatic device based on an air gun to simulate the blast shock wave, and established a BTBI cell model by using primary cultured rat CNS cortical tissue and human CNS cortical tissue. They found that the expression of reactive astrocyte markers GFAP and protease matrix metallopeptidase 9 in human central nervous system cells significantly increased 24 h after shock wave stimulation. Interestingly, they found that human astrocyte were more responsive to injury than rat derived astrocyte. The ABS model has its own important shortcomings. First, the physical characteristics of the gas-driven shock wave may be different from that of the explosion shock wave; second, the diaphragm fragment may impact the subjects; third, the efflux effect generated near the tube outlet may have impacted the subjects (53). The main advantages of the ABS model are its high safety, indoor operation, and greatly reduced external interference. Shock waves of different sizes can be generated by adjusting the material of the diaphragm (64–66). The ABS model is the most widely used model in BTBI research.

5. Repeated minor trauma injury models (r-mTBI)

R-mTBI usually occurs in contact sports (eg. boxing, basketball, football, rugby) and in domestic violence (12, 67). There is growing evidence that repeated concussions can lead to behavioral abnormalities and pathological changes, and several models of r-mTBI have been established. These include the CCI, WD, FPI Blast-TBI, and Cell stretch injury models (68–72). R-mTBI over a short period of time can cause diffuse axonal injury and chronic neuroinflammation. These pathophysiological phenomena are closely related to neurodegenerative diseases such as Alzheimer's disease and Parkinson's syndrome. The microtubule associated protein tau is an indispensable part of the pathogenesis of Alzheimer's disease (AD) and several related diseases called tau disease, where tau is deposited in the affected brain regions. Research has shown that changes in soluble tau proteins, including phosphorylation, are involved in inducing neuronal death. Therefore, the method of reducing tau phosphorylation may exert the neuroprotective effect of neurodegenerative diseases such as AD by reducing the generation of amyloid protein (73). Research has shown that tau phosphorylation may be regulated by metal ions such as iron, zinc, and copper, which are themselves associated with neurodegenerative diseases such as aging and Alzheimer's disease (74). The results of most studies show that r-mTBI will lead to pathological tau formation, metal homeostasis disorder, tau hyperphosphorylation, astrocyte proliferation, microglia proliferation and brain atrophy, as well as progressive learning and cognitive disorders that continue to develop for a long time after the injury stops. Of course, it is important to emphasize that not all r-mTBI studies have reported tau pathology, which may be because TBI models There are differences in experimental design parameters, species, animal age, and detected time points (74). Although mild brain damage is often overlooked, with the intensification of population aging, r-mTBI will be increasingly studied by researchers. Therefore, developing sufficient r-mTBI models and considering more factors such as species, gender, age, acute phase, subacute phase, and chronic phase, provides more sufficient evidence on how r-mTBI leads to pathological tau formation, metal homeostasis disorders, and motor and cognitive deficits, thereby jointly leading to neurodegenerative diseases.

6. Conclusions and future directions

Although the application of TBI models in the study of brain injury has made some progress, there are still some insuperable shortcomings (Table 1). The brains of commonly used TBI model animals (especially rodents) are physiologically similar to human brains, to a certain extent, but there are still significant differences in brain structure and function, such as brain geometry, cranial Angle, cyclotron complexity, and gray to white matter ash ratio (12, 41). Many TBI model studies strictly did not measure physiological variables before and after TBI, including CO2, and O2 partial pressures, pH, blood pressure and brain temperature, etc. These variables are important in determining the body's pathophysiological response to injury and treatment. In addition, age, sex and species have an impact on TBI results (3, 4, 76, 77, 79, 80), and more research is needed. The limitation of *in vitro* TBI models is that tissue cells may produce harmful stress responses *in vitro*. Secondly, tissue cells may have been damaged in the process of sampling, which may influence experimental tissue damage to a certain extent. *In vitro* TBI models should focus on reducing the influence of extracellular environment (such as blood, activated macrophages, etc.) on nerve cells and reducing the damage caused by tissue cells in the process of sampling (75, 78, 81–83). Sometimes studies based on *in vitro* and *in vivo* models produce conflicting results, but this does not mean that *in vitro* models are inaccurate and may relate to environmental differences (e.g., inflammatory responses, temperature regulation, oxygenation, or local ion concentrations) (12, 54, 82, 84–86). Both types of TBI models have advantages and disadvantages. Therefore, different types of *in vitro* and *in vivo* TBI models should be combined, when studying a new treatment or drug, to simulate different

TABLE 1 Characteristics of the commonly used TBI animal and cell models.

Types of TBI models			Types of injury	Limitations	Advantages
Mechanical injury models	Animal models	Feeney (16–20, 75)	Contusion cerebral cortex; Cerebral concussion	A bone window is required High fatality rate	Simple methods; Easy control
		Shohami (21–24)	Induced mixed; Diffuse injury	High fatality rate; Poor repeatability	Simple methods; Low cost
		Marmarou (10, 14, 15, 21)	Diffuse injury; Axonal injury	High fatality rate	Simple methods; Easy control
		CCI (24, 25, 30–32, 68)	Cortical loss; Cerebral concussion	Expensive equipment; A bone window is required	Good repeatability Accuracy of injury
	Cell models	Transection (29–31)	Axonal damage and puncture wounds	Need for standardization	No special equipment and instrument conditions are required
		Stretch (32–39, 76–78)	Axonal damage to nerve cells	Complex instrument; Expensive equipment	Precise damage to specific areas of the cell
Pressure injury models	Animal models	FPI (40–47, 70)	Intracranial hemorrhage and brain swelling	The mechanism of injury is different from the clinical situation	Good repeatability; High stability
		PBBI (48, 49)	Intracranial hemorrhage and increased intracranial pressure	Standardization and special equipment are required	The injury was similar to the clinical one
	Cell models	Compression (50, 51)	Increased intracranial pressure was replicated	Pressure control device is required	Simple methods; Easy control of conditions
		Vacuum helper cell damage (36, 52)	Axonal damage to nerve cells	Pressure control needs to be refined	Accuracy of injury; Simple methods
Blast injury models	Animal models	BTBI model (54–66)	Blast shock wave damage	Special equipment; Jet flow effect	The injuries were similar to war wounds
	Cell models	ABS cell model (60, 61, 63, 66)	Blast shock wave damage	Diaphragm fragment shadow	Indoor operation; High safety
R-mTBI (12, 67–72, 74)			Diffuse brain injury	Need for standardization	The injury was similar to the clinical one

pathobiological reactions caused during injury. Cross-validation in this way can make the experimental results more robust and reliable, and reduce the false positive neuroprotective effect of some drugs or treatments.

Author contributions

QZ and FX designed the overall project. FX, HoL, and QZ analyzed the data and wrote the manuscript. HuL, and JZ revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Ruff RL, Riechers RG. Effective treatment of traumatic brain injury: learning from experience. *JAMA*. (2012) 308:2032–3. doi: 10.1001/jama.2012.14008

2. Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol*. (2022) 21:1004–60. doi: 10.1016/S1474-4422(22)00309-X

3. 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. doi: 10.15585/mmwr.ss6609a1

4. Majdan M, Plancikova D, Brazinova A, Rusnak M, Nieboer D, Feigin V, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Health*. (2016) 1:e76–83. doi: 10.1016/S2468-2667(16)30017-2

5. Jiang JY, Gao GY, Feng JF, Mao Q, Chen LG, Yang XF, et al. Traumatic brain injury in China. *Lancet Neurol*. (2019) 18:286–95. doi: 10.1016/S1474-4422(18)30469-1

6. Hicks AJ, Ponsford JL, Spitz G, Dore V, Krishnadas N, Roberts C, et al. β-Amyloid and tau imaging in chronic traumatic brain injury: a cross-sectional study. *Neurology*. (2022) 99:e1131–41. doi: 10.1212/WNL.0000000000200857

7. VanItallie TB. Traumatic brain injury (TBI) in collision sports: possible mechanisms of transformation into chronic traumatic encephalopathy (CTE). *Metab Clin Exp*. (2019) 100:153943. doi: 10.1016/j.metabol.2019.07.007

8. Golub VM, Reddy DS. Post-traumatic epilepsy and comorbidities: advanced models, molecular mechanisms, biomarkers, and novel therapeutic interventions. *Pharmacol Rev*. (2022) 74:387–438. doi: 10.1124/pharmrev.121.000375

9. Shi K, Zhang J, Dong JF, Shi FD. Dissemination of brain inflammation in traumatic brain injury. *Cell Mol Immunol*. (2019) 16:523–30. doi: 10.1038/s41423-019-0213-5

10. Ebrahimi H, Kazem Nezhad S, Farmoudeh A, Babaei A, Ebrahimnejad P, Akbari E, et al. Design and optimization of metformin-loaded solid lipid nanoparticles for neuroprotective effects in a rat model of diffuse traumatic brain injury: a biochemical, behavioral, and histological study. *Eur J Pharmaceut Biopharmaceut Off J Arbeitsgemeinschaft Pharmazeutische Verfahrenstechnik eV*. (2022) 181:122–35. doi: 10.1016/j.ejpb.2022.10.018

11. Feeney DM, Boyeson MG, Linn RT, Murray HM, Dail WG. Responses to cortical injury: I. methodology and local effects of contusions in the rat. *Brain Res*. (1981) 211:67–77. doi: 10.1016/0006-8993(81)90067-6

12. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. *Nat Rev Neurosci*. (2013) 14:128–42. doi: 10.1038/nrn3407

13. Khellaf A, Khan DZ, Helmy A. Recent advances in traumatic brain injury. *J Neurol*. (2019) 266:2878–89. doi: 10.1007/s00415-019-09541-4

14. Marmarou A, Foda MA, van den Brink W, Campbell J, Kita H, Demetriadou K. A new model of diffuse brain injury in rats. Part I: pathophysiology and biomechanics. *J Neurosurg*. (1994) 80:291–300. doi: 10.3171/jns.1994.80.2.0291

15. Chakraborty N, Hammamieh R, Gautam A, Miller SA, Condlin ML, Jett M, et al. TBI weight-drop model with variable impact heights differentially perturbs hippocampus-cerebellum specific transcriptomic profile. *Exp Neurol*. (2021) 335:113516. doi: 10.1016/j.expneurol.2020.113516

16. Pang AL, Xiong LL, Xia QJ, Liu F, Wang YC, Liu F, et al. Neural stem cell transplantation is associated with inhibition of apoptosis, Bcl-xL Upregulation, and recovery of neurological function in a rat model of traumatic brain injury. *Cell Transplant*. (2017) 26:1262–75. doi: 10.1177/0963689717715168

17. Chen X, Wu S, Chen C, Xie B, Fang Z, Hu W, et al. Omega-3 polyunsaturated fatty acid supplementation attenuates microglial-induced inflammation by inhibiting the HMGB1/TLR4/NF-κB pathway following experimental traumatic brain injury. *J Neuroinflammation*. (2017) 14:143. doi: 10.1186/s12974-017-0917-3

18. Jia J, Chen F, Wu Y. Recombinant PEP-1-SOD1 improves functional recovery after neural stem cell transplantation in rats with traumatic brain injury. *Exp Ther Med*. (2018) 15:2929–35. doi: 10.3892/etm.2018.5781

19. He H, Liu W, Zhou Y, Liu Y, Weng P, Li Y, et al. Sevoflurane post-conditioning attenuates traumatic brain injury-induced neuronal apoptosis by promoting autophagy via the PI3K/AKT signaling pathway. *Drug Des Devel Ther*. (2018) 12:629–38. doi: 10.2147/DDDT.S158313

20. Wang Z, Li J, Wang A, Wang Z, Wang J, Yuan J, et al. Sevoflurane inhibits traumatic brain injury-induced neuron apoptosis via EZH2-Downregulated KLF4/p38 Axis. *Front Cell Dev Biol*. (2021) 9:658720. doi: 10.3389/fcell.2021.658720

21. Bodnar CN, Roberts KN, Higgins EK, Bachstetter AD. A systematic review of closed Head injury models of mild traumatic brain injury in mice and rats. *J Neurotrauma*. (2019) 36:1683–706. doi: 10.1089/neu.2018.6127

22. Shapira Y, Shohami E, Sidi A, Soffer D, Freeman S, Cotev S. Experimental closed head injury in rats: mechanical, pathophysiologic, and neurologic properties. *Crit Care Med*. (1988) 16:258–65. doi: 10.1097/00003246-198803000-00010

23. Flierl MA, Stahel PF, Beauchamp KM, Morgan SJ, Smith WR, Shohami E. Mouse closed head injury model induced by a weight-drop device. *Nat Protoc*. (2009) 4:1328–37. doi: 10.1038/nprot.2009.148

24. Ma X, Aravind A, Pfister BJ, Chandra N, Haorah J. Animal models of traumatic brain injury and assessment of injury severity. *Mol Neurobiol*. (2019) 56:5332–45. doi: 10.1007/s12035-018-1454-5

25. Lighthall JW. Controlled cortical impact: a new experimental brain injury model. *J Neurotrauma*. (1988) 5:1–15. doi: 10.1089/neu.1988.5.1

26. Zhao QH, Xie F, Guo DZ, Ju FD, He J, Yao TT, et al. Hydrogen inhalation inhibits microglia activation and neuroinflammation in a rat model of traumatic brain injury. *Brain Res*. (2020) 1748:147053. doi: 10.1016/j.brainres.2020.147053

27. Hu J, Wang X, Chen X, Fang Y, Chen K, Peng W, et al. Hydroxychloroquine attenuates neuroinflammation following traumatic brain injury by regulating the TLR4/NF-κB signaling pathway. *J Neuroinflammation*. (2022) 19:71. doi: 10.1186/s12974-022-02430-0

28. Shultz SR, McDonald SJ, Vonder Haar C, Meconi A, Vink R, van Donkelaar P, et al. The potential for animal models to provide insight into mild traumatic brain injury: translational challenges and strategies. *Neurosci Biobehav Rev*. (2017) 76:396–414. doi: 10.1016/j.neubiorev.2016.09.014

29. Faden AI, Movsesyan VA, Knoblach SM, Ahmed F, Cernak I. Neuroprotective effects of novel small peptides *in vitro* and after brain injury. *Neuropharmacology*. (2005) 49:410–24. doi: 10.1016/j.neuropharm.2005.04.001

30. Cengiz N, Oztürk G, Erdoğan E, Him A, Oğuz EK. Consequences of neurite transection *in vitro*. *J Neurotrauma*. (2012) 29:2465–74. doi: 10.1089/neu.2009.0947

31. Liu W, Chen Y, Meng J, Wu M, Bi F, Chang C, et al. Ablation of caspase-1 protects against TBI-induced pyroptosis *in vitro* and *in vivo*. *J Neuroinflammation*. (2018) 15:48. doi: 10.1186/s12974-018-1083-y

32. Saykally JN, Hatic H, Keeley KL, Jain SC, Ravindranath V, Citron BA. Withania somnifera extract protects model neurons from *in vitro* traumatic injury. *Cell Transplant*. (2017) 26:1193–201. doi: 10.1177/0963689717714320

33. Cater HL, Sundstrom LE, Morrison B. Temporal development of hippocampal cell death is dependent on tissue strain but not strain rate. *J Biomech*. (2006) 39:2810–8. doi: 10.1016/j.jbiomech.2005.09.023

34. Salvador E, Burek M, Förster CY. Stretch and/or oxygen glucose deprivation (OGD) in an *in vitro* traumatic brain injury (TBI) model induces calcium alteration and inflammatory cascade. *Front Cell Neurosci*. (2015) 9:323. doi: 10.3389/fncel.2015.00323

35. Yap YC, King AE, Guijt RM, Jiang T, Blizzard CA, Breadmore MC, et al. Mild and repetitive very mild axonal stretch injury triggers cytoskeletal mislocalization and growth cone collapse. *PLoS One*. (2017) 12:e0176997. doi: 10.1371/journal.pone.0176997

36. Shrirao AB, Kung FH, Omelchenko A, Schloss RS, Boustany NN, Zahn JD, et al. Microfluidic platforms for the study of neuronal injury *in vitro*. *Biotechnol Bioeng*. (2018) 115:815–30. doi: 10.1002/bit.26519

37. Kumaria A. *In vitro* models as a platform to investigate traumatic brain injury. *Alternat Lab Anim ATLA*. (2017) 45:201–11. doi: 10.1177/026119291704500405

38. Chaves RS, Tran M, Holder AR, Balcer AM, Dickey AM, Roberts EA, et al. Amyloidogenic processing of amyloid precursor protein drives stretch-induced disruption of axonal transport in hiPSC-derived neurons. *J Neurosci Off J Soc Neurosci*. (2021) 41:10034–53. doi: 10.1523/JNEUROSCI.2553-20.2021

39. Wu YH, Rosset S, Lee TR, Dragunow M, Park T, Shim V. *In vitro* models of traumatic brain injury: a systematic review. *J Neurotrauma*. (2021) 38:2336–72. doi: 10.1089/neu.2020.7402

40. Dixon CE, Lyeth BG, Povlishock JT, Findling RL, Hamm RJ, Marmarou A, et al. A fluid percussion model of experimental brain injury in the rat. *J Neurosurg*. (1987) 67:110–9. doi: 10.3171/jns.1987.67.1.0110

41. Morales DM, Marklund N, Lebold D, Thompson HJ, Pitkanen A, Maxwell WL, et al. Experimental models of traumatic brain injury: do we really need to build a better mousetrap? *Neuroscience*. (2005) 136:971–89. doi: 10.1016/j.neuroscience.2005.08.030

42. Alder J, Fujioka W, Lifshitz J, Crockett DP, Thakker-Varia S. Lateral fluid percussion: model of traumatic brain injury in mice. *J Visual Exp JoVE*. (2011) 54:3063. doi: 10.3791/3063

43. Liu YR, Cardamone L, Hogan RE, Gregoire MC, Williams JP, Hicks RJ, et al. Progressive metabolic and structural cerebral perturbations after traumatic brain injury: an *in vivo* imaging study in the rat. *J Nucl Med Off Publ Soc Nucl Med*. (2010) 51:1788–95. doi: 10.2967/jnumed.110.078626

44. Evans LP, Newell EA, Mahajan M, Tsang SH, Ferguson PJ, Mahoney J, et al. Acute vitreoretinal trauma and inflammation after traumatic brain injury in mice. *Ann Clin Transl Neurol*. (2018) 5:240–51. doi: 10.1002/acn3.523

45. Song H, Chen C, Kelley B, Tomasevich A, Lee H, Dolle JP, et al. Traumatic brain injury recapitulates developmental changes of axons. *Prog Neurobiol*. (2022) 217:102332. doi: 10.1016/j.pneurobio.2022.102332

46. Wangler LM, Bray CE, Packer JM, Tapp ZM, Davis AC, O'Neil SM, et al. Amplified gliosis and interferon-associated inflammation in the aging brain following diffuse traumatic brain injury. *J Neurosci Off J Soc Neurosci*. (2022) 42:9082–96. doi: 10.1523/JNEUROSCI.1377-22.2022

47. Kabadi SV, Hilton GD, Stoica BA, Zapple DN, Faden AI. Fluid-percussion-induced traumatic brain injury model in rats. *Nat Protoc*. (2010) 5:1552–63. doi: 10.1038/nprot.2010.112

48. Davis AR, Shear DA, Chen Z, Lu XC, Tortella FC. A comparison of two cognitive test paradigms in a penetrating brain injury model. *J Neurosci Methods*. (2010) 189:84–7. doi: 10.1016/j.jneumeth.2010.03.012

49. Shear DA, Lu XC, Pedersen R, Wei G, Chen Z, Davis A, et al. Severity profile of penetrating ballistic-like brain injury on neurofunctional outcome, blood-brain barrier permeability, and brain edema formation. *J Neurotrauma*. (2011) 28:2185–95. doi: 10.1089/neu.2011.1916

50. Popova D, Karlsson J, Jacobsson SOP. Comparison of neurons derived from mouse P19, rat PC12 and human SH-SY5Y cells in the assessment of chemical- and toxin-induced neurotoxicity. *BMC Pharmacol Toxicol*. (2017) 18:42. doi: 10.1186/s40360-017-0151-8

51. Smith ME, Eskandari R. A novel technology to model pressure-induced cellular injuries in the brain. *J Neurosci Methods*. (2018) 293:247–53. doi: 10.1016/j.jneumeth.2017.10.004

52. Zhou B, Yu P, Lin MY, Sun T, Chen Y, Sheng ZH. Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits. *J Cell Biol*. (2016) 214:103–19. doi: 10.1083/jcb.201605101

53. Kovacs SK, Leonessa F, Ling GS. Blast TBI models, neuropathology, and implications for seizure risk. *Front Neurol*. (2014) 5:47. doi: 10.3389/fneur.2014.00047

54. Risling M, Plantman S, Angeria M, Rostami E, Bellander BM, Kirkegaard M, et al. Mechanisms of blast induced brain injuries, experimental studies in rats. *Neuro Image*. (2011) 54:S89–97. doi: 10.1016/j.neuroimage.2010.05.031

55. Aravind A, Ravula AR, Chandra N, Pfister BJ. Behavioral deficits in animal models of blast traumatic brain injury. *Front Neurol*. (2020) 11:990. doi: 10.3389/fneur.2020.00990

56. Rodriguez UA, Zeng Y, Deyo D, Parsley MA, Hawkins BE, Prough DS, et al. Effects of mild blast traumatic brain injury on cerebral vascular, Histopathological, and behavioral outcomes in rats. *J Neurotrauma*. (2018) 35:375–92. doi: 10.1089/neu.2017.5256

57. Kobeissy F, Mondello S, Tümer N, Toklu HZ, Whidden MA, Kirichenko N, et al. Assessing neuro-systemic & behavioral components in the pathophysiology of blast-related brain injury. *Front Neurol*. (2013) 4:186. doi: 10.3389/fneur.2013.00186

58. Gama Sosa MA, De Gasperi R, Perez Garcia GS, Sosa H, Searcy C, Vargas D, et al. Lack of chronic neuroinflammation in the absence of focal hemorrhage in a rat model of low-energy blast-induced TBI. *Acta Neuropathol Commun*. (2017) 5:80. doi: 10.1186/s40478-017-0483-z

59. Tchantchou F, Fourney WL, Leiste UH, Vaughan J, Rangghran P, Puche A, et al. Neuropathology and neurobehavioral alterations in a rat model of traumatic brain injury to occupants of vehicles targeted by underbody blasts. *Exp Neurol*. (2017) 289:9–20. doi: 10.1016/j.expneurol.2016.12.001

60. Campos-Pires R, Koziakova M, Yonis A, Pau A, Macdonald W, Harris K, et al. Xenon protects against blast-induced traumatic brain injury in an *in vitro* model. *J Neurotrauma*. (2018) 35:1037–44. doi: 10.1089/neu.2017.5360

61. Arun P, Spadaro J, John J, Gharavi RB, Bentley TB, Nambiar MP. Studies on blast traumatic brain injury using *in-vitro* model with shock tube. *Neuroreport*. (2011) 22:379–84. doi: 10.1097/WNR.0b013e328346b138

62. Vogel EW 3rd, Morales FN, Meaney DF, Bass CR, Morrison B 3rd. Phosphodiesterase-4 inhibition restored hippocampal long term potentiation after primary blast. *Exp Neurol*. (2017) 293:91–100. doi: 10.1016/j.expneurol.2017.03.025

63. Ravin R, Blank PS, Busse B, Ravin N, Vira S, Bezrukov L, et al. Blast shockwaves propagate Ca(2+) activity via purinergic astrocyte networks in human central nervous system cells. *Sci Rep*. (2016) 6:25713. doi: 10.1038/srep25713

64. Rosenfeld JV, McFarlane AC, Bragge P, Armonda RA, Grimes JB, Ling GS. Blast-related traumatic brain injury. *Lancet Neurol*. (2013) 12:882–93. doi: 10.1016/S1474-4422(13)70161-3

65. Snapper DM, Reginauld B, Liaudanskaya V, Fitzpatrick V, Kim Y, Georgakoudi I, et al. Development of a novel bioengineered 3D brain-like tissue for studying primary blast-induced traumatic brain injury. *J Neurosci Res*. (2023) 101:3–19. doi: 10.1002/jnr.25123

66. Campos-Pires R, Yonis A, Macdonald W, Harris K, Edge CJ, Mahoney PF, et al. A novel *in vitro* model of blast traumatic brain injury. *J Vis Exp JoVE*. (2018). doi: 10.3791/58400. doi:10.3791/58400

67. Pham L, Wright DK, O'Brien WT, Bain J, Huang C, Sun M, et al. Behavioral, axonal, and proteomic alterations following repeated mild traumatic brain injury: novel insights using a clinically relevant rat model. *Neurobiol Dis*. (2021) 148:105151. doi: 10.1016/j.nbd.2020.105151

68. Yu F, Shukla DK, Armstrong RC, Marion CM, Radomski KL, Selwyn RG, et al. Repetitive model of mild traumatic brain injury produces cortical abnormalities detectable by magnetic resonance diffusion imaging, histopathology, and behavior. *J Neurotrauma*. (2017) 34:1364–81. doi: 10.1089/neu.2016.4569

69. Kane MJ, Angoa-Pérez M, Briggs DI, Viano DC, Kreipke CW, Kuhn DM. A mouse model of human repetitive mild traumatic brain injury. *J Neurosci Methods*. (2012) 203:41–9. doi: 10.1016/j.jneumeth.2011.09.003

70. Shultz SR, MacFabe DF, Foley KA, Taylor R, Cain DP. Sub-concussive brain injury in the long-Evans rat induces acute neuroinflammation in the absence of behavioral impairments. *Behav Brain Res*. (2012) 229:145–52. doi: 10.1016/j.bbr.2011.12.015

71. Skotak M, Wang F, Chandra N. An *in vitro* injury model for SH-SY5Y neuroblastoma cells: effect of strain and strain rate. *J Neurosci Methods*. (2012) 205:159–68. doi: 10.1016/j.jneumeth.2012.01.001

72. Ondek K, Brevnova O, Jimenez-Ornelas C, Vergara A, Zwienenberg M, Gurkoff G. A new model of repeat mTBI in adolescent rats. *Exp Neurol*. (2020) 331:113360. doi: 10.1016/j.expneurol.2020.113360

73. Hanger DP, Anderton BH, Noble W. Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. *Trends Mol Med*. (2009) 15:112–9. doi: 10.1016/j.molmed.2009.01.003

74. Juan SMA, Daglas M, Adlard PA. Tau pathology, metal Dyshomeostasis and repetitive mild traumatic brain injury: an unexplored link paving the way for Neurodegeneration. *J Neurotrauma*. (2022) 39:902–22. doi: 10.1089/neu.2021.0241

75. Adamchik Y, Frantseva MV, Weisspapir M, Carlen PL, Perez Velazquez JL. Methods to induce primary and secondary traumatic damage in organotypic hippocampal slice cultures. *Brain Res Brain Res Protoc*. (2000) 5:153–8. doi: 10.1016/s1385-299x(00)00007-6

76. Puntambekar SS, Saber M, Lamb BT, Kokiko-Cochran ON. Cellular players that shape evolving pathology and neurodegeneration following traumatic brain injury. *Brain Behav Immun*. (2018) 71:9–17. doi: 10.1016/j.bbi.2018.03.033

77. Prexl O, Bruckbauer M, Voelckel W, Grottke O, Ponschab M, Maegele M, et al. The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. *Scand J Trauma Resusc Emerg Med*. (2018) 26:20. doi: 10.1186/s13049-018-0487-0

78. Morrison B 3rd, Cater HL, Benham CD, Sundstrom LE. An *in vitro* model of traumatic brain injury utilising two-dimensional stretch of organotypic hippocampal slice cultures. *J Neurosci Methods*. (2006) 150:192–201. doi: 10.1016/j.jneumeth.2005.06.014

79. Ercole A, Magnoni S, Vegliante G, Pastorelli R, Surmacki J, Bohndiek SE, et al. Current and emerging Technologies for Probing Molecular Signatures of traumatic brain injury. *Front Neurol*. (2017) 8:450. doi: 10.3389/fneur.2017.00450

80. Shah EJ, Gurdziel K, Ruden DM. Mammalian models of traumatic brain injury and a place for Drosophila in TBI research. *Front Neurosci*. (2019) 13:409. doi: 10.3389/fnins.2019.00409

81. Vink R. Large animal models of traumatic brain injury. *J Neurosci Res*. (2018) 96:527–35. doi: 10.1002/jnr.24079

82. Morrison B 3rd, Elkin BS, Dollé JP, Yarmush ML. *In vitro* models of traumatic brain injury. *Annu Rev Biomed Eng*. (2011) 13:91–126. doi: 10.1146/annurev-bioeng-071910-124706

83. Liu N, Li Y, Jiang Y, Shi S, Niamnud A, Vodovoz SJ, et al. Establishment and application of a novel *in vitro* model of microglial activation in traumatic brain injury. *J Neurosci Off J Soc Neurosci*. (2022) 43:319–32. doi: 10.1523/JNEUROSCI.1539-22.2022

84. Elkin BS, Morrison B. Region-specific tolerance criteria for the living brain. *Stapp Car Crash J*. (2007) 51:127–38. doi: 10.4271/2007-22-0005

85. Thelin EP, Hall CE, Gupta K, Carpenter KLH, Chandran S, Hutchinson PJ, et al. Elucidating pro-inflammatory cytokine responses after traumatic brain injury in a human stem cell model. *J Neurotrauma*. (2018) 35:341–52. doi: 10.1089/neu.2017.5155

86. Estrada-Rojo F, Martínez-Tapia RJ, Estrada-Bernal F, Martínez-Vargas M, Perez-Arredondo A, Flores-Avalos L, et al. Models used in the study of traumatic brain injury. *Rev Neurosci*. (2018) 29:139–49. doi: 10.1515/revneuro-2017-0028

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An exhaustive analysis of post-traumatic brain injury dementia using bibliometric methodologies

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Background: It is widely accepted that traumatic brain injury (TBI) increases the risk of developing long-term dementia, although some controversies surrounding this topic exist. Annually, approximately 69 million individuals suffer from TBI all around the world. Such a large population of TBI patients could lead to a future surge in the number of dementia patients. Due to the potentially severe consequences of TBI, various research projects on post-TBI dementia have emerged worldwide. Therefore, it is essential to comprehend the current status and development of post-TBI dementia for future research.

Objective: The purpose of the study was to provide an overview of the field and identify hotspots, research frontiers, and future research trends for post-TBI dementia.

Methods: Articles related to post-TBI dementia were retrieved from the Web of Science Core Collection for the period between 2007 and 2022, and analyzing them based on factors such as citations, authors, institutions, countries, journals, keywords, and references. Data analysis and visualization were conducted using VOSviewer, CiteSpace, and an online bibliometric platform (https://bibliometric.com).

Results: From 2007 to 2022, we obtained a total of 727 articles from 3,780 authors and 1,126 institutions across 52 countries, published in 262 journals. These articles received a total of 29,353 citations, citing 25,713 references from 3,921 journals. Over the last 15 years, there has been a significant upward trend in both publications and citations. The most productive country was the United States, the most productive institution was Boston University, and the most productive author was McKee AC. *Journal of Neurotrauma* has been identified as the periodical with the greatest number of publications. Three clusters were identified through cluster analysis of keywords. A burst in the use of the term "outcome" in 2019 is indicative of a future research hotspot. The timeline view of references showed 14 clusters, of which the first 4 clusters collected the majority of papers. The first 4 clusters were "chronic traumatic encephalopathy," "age of onset," "tauopathy," and "cognitive decline," respectively, suggesting some areas of interest in the field.

Conclusion: The subject of post-TBI dementia has raised much interest from scientists. Notably, America is at the forefront of research in this area. Further collaborative research between different countries is imperative. Two topical issues in this field are "The association between TBI and dementia-related alterations" and "chronic traumatic encephalopathy (CTE)." Studies on clinical

manifestation, therapy, pathology, and pathogenic mechanisms are also popular in the field.

KEYWORDS

brain injuries, traumatic, dementia, chronic traumatic encephalopathy, Alzheimer disease, bibliometric

Introduction

Traumatic brain injury (TBI), caused by striking, knocking, shaking the head, and so on, could lead to several harmful effects on various aspects of daily life, including executive capabilities, interpersonal relationships, mindset, behavioral modes, and learning abilities.[1] Several researches suggested that TBI might be a risk factor for the development of dementia. Tagge et al. (1) found that closed TBI could induce acute and sustained impairment to axonal conduction velocity in the hippocampus. Stopa et al. (2) proposed that TBI patients had an increased risk of developing dementia. They conducted a retrospective cohort study involving 24,846 patients with a follow-up of 10 years and found that patients with TBI had a hazard ratio (HR) of 2.2 for developing dementia. Another cohort study conducted in Denmark by Osler et al. (3) supported Stopa et al.'s (2), highlighting an even stronger correlation between TBI and early-onset dementia (diagnosed at age 60 and before, HR 5.49). TBI patients may have a higher prevalence of Alzheimer's disease (AD), Vascular dementia (VD), Parkinson's disease (PD), and mild cognitive impairment (MCI) (4, 5). The 2020 report by the Lancet Commission expressly suggested that TBI could raise the possibility of the onset of dementia with a population attributable fraction (PAF) of 3.4% (6). In sum, it is widely accepted in mainstream literature that TBI is a significant risk factor for dementia despite some controversies in the field (7–10).

It is estimated that around 69 million people worldwide suffer from TBI annually (11). Such a large population of TBI patients might lead to a future surge in the number of dementia patients, with great implications for societies. As such, investigations into post-TBI dementia hold significant importance from both medical and societal standpoints. A thorough comprehension of the discipline's current state and the progress of developments would be crucial for future studies. Additionally, identifying the pivotal literature and potential avenues of research could assist scholars in promptly ascertaining their research directions.

Bibliometrics is a discipline that assesses academic productivity using quantitative means, which provides plenty of statistical parameters, like publication count, citation count, H-index, and impact factor (IF) (12). The bibliometric analysis gives us an efficient means of grasping an overview of a given field, discerning its development trajectory, and highlighting notable scholars and work. Substantial aspects of the science domain could be described in the form of scientific networks, like the maps of co-authorship, co-occurrence, citation, and co-citation. These networks are beneficial to our intuitive understanding of the various changes that have taken place in reality (13). Bibliometric mapping is a momentous part of bibliometric analysis, and several tools available could assist us in mapping, like VOSviewer and CiteSpace. Bibliometric mapping could be divided into two parts: (1) the construction of maps and (2) the visualization of graphics (13). VOSviewer is a software designed for bibliometric network construction and visualization, with a particular focus on the graphical representation of maps. It is adept at the diagrammatic processing of large data sets efficiently (13). CiteSpace, developed by Chaomei Chen's team, could visualize the network of co-citations and facilitate the exploration of the progression of subjects (14, 15). Bibliometric analyses, employing software tools, are widely utilized in the medical field (16–18).

Following our preliminary search, we have identified a rapid increase in the number of publications after 2007 in the discipline of post-TBI dementia (as shown in Supplementary Figure S1). Therefore, we made the bibliometric analysis based on publications about post-TBI dementia from 2007 to 2022 to gain insight into the current status and progress of this discipline. We intend to answer: What about the distribution of scientific productivity in this area? Which are the research hotspots in the field? What will be the future trends in the discipline? Our study aims to provide a quick panoramic view of the field to assist researchers in identifying areas of interest for further exploration.

Method

Data source

The Clarivate Analytic's Web of Science Core Collection (WOSCC) database was selected as our primary data source. To ensure the accuracy and quality of retrieval, the Citation Index was set to Science Citation Index Expanded (SCIE), one of the subdatabases of WOSCC which is a comprehensive, multi-disciplinary database encompassing more than 8,600 specialized journals (17). Clarivate Analytic's Web of Science (WOS), as one of the most influential platforms in terms of retrieval, access, and analysis of citations, has offered great support to scientific researchers in various fields and made tremendous contributions to the development of natural science. Moreover, there is a widespread application of WOS in the field of medicine (16).

Search strategy

The retrieval formula was "TS = [("traumatic brain injury" OR "chronic traumatic encephalopathy") AND ("dementia" OR

1 https://www.cdc.gov/traumaticbraininjury/health-disparities-tbi.html

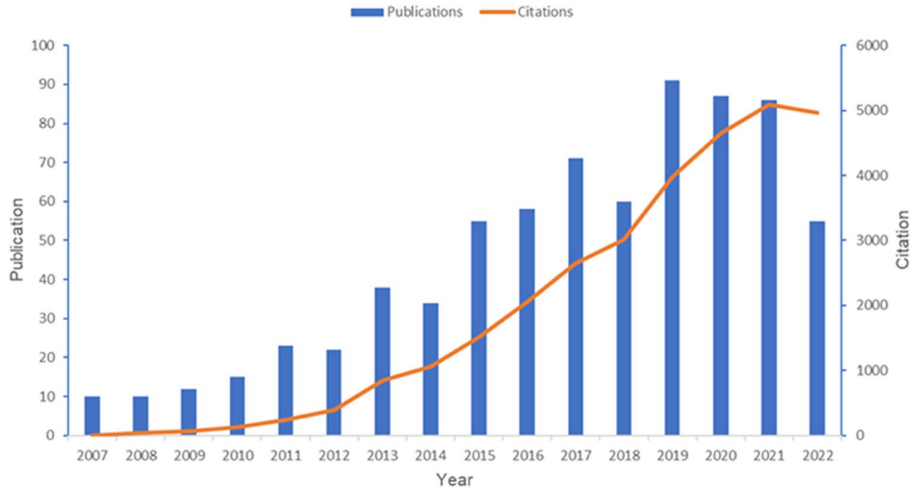

FIGURE 1
Overview of publications in the field of post-TBI dementia from 2007 to 2022. This figure is generated using Microsoft Excel 2019.

"Alzheimer's disease")]." "Year of publication" was set from 2007 to 2022. Only original researches were selected. The retrieval was made on October 12, 2022, and 1,590 documents were gained. The result was checked by Citespace to remove the duplication. The rest was scrutinized by three researchers to exclude articles that were unrelated to the topic or of which the primary content was not about post-TBI dementia. Lastly, a total of 727 articles were retained as the basis for the follow-on analysis. Supplementary Figure S2 depicts the flowchart of data acquisition.

Data analysis

The related analysis was conducted based on Microsoft Excel 2019, CiteSpace 6.1.R2 (64-bit), VOSviewer 1.6.18, and an online analysis platform.[2]

Based on CiteSpace, we performed network analyses of the co-authorship of countries and institutions, and the co-citation of references. The parameters were set as follows: Time slice (2007 to 2022), Years per slice (1), Link (Strength: Cosine, Scope: Within Slices), and Selection Criteria (g-index: $k = 25$). VOSviewer was used to conduct network analyses of the co-authorship of organizations and authors, the co-occurrence of all keywords, the citation of sources, and the co-citation of cited authors. Each node in the map, generated by the above two pieces of software, represents a country, institute, author, or other subject, of which the size reflects the frequency of appearance. The edges represent the connection between nodes, and their thickness denotes the tightness of the association. And the colors of the nodes represent the clusters they belong to. Moreover, some indicators, such as total link strength (TLS) for VOSviewer and betweenness centrality (BC) for CiteSpace, measure the significance of a node within a given network (17, 18). Besides, when we implemented the co-citation analysis, the newly published papers were likely to be underestimated because of their relatively poor citations. Burst detection, which could recognize the emergent words no matter how many citations they had, is conducive to solving the problem (15). We conducted the keyword-burst detection analysis to catch some significant and emergent subject matters. In addition, we performed analyses of the distribution of annual publications across countries and international cooperation with the help of the web https://bibliometric.com. Microsoft Excel 2019 was used for data reorganization.

Results

General data

A total of 727 articles were retrieved, between 2007 and 2022, from 1,126 institutions and 52 countries, authored by 3,780 individuals, and published in 262 periodicals, which cited 25,713 references from 3,921 journals. Cumulatively, these publications have been cited 29,353 times. Figure 1 shows the publication and citation of papers in this field year after year. In general, the number of annual publications showed an upward trend despite the fluctuations from 2007 to 2019 and reached a stable level for the next few years (around 90 articles per year). Concerning the situation of citations, we could find a strong uptrend during the past 15 years. The above findings demonstrate the increased scholarly interest in post-TBI dementia in recent years, highlighting its position as a hotspot in the field of TBI.

Countries and institutions analysis

We analyzed the contribution of each country to the annual number of publications, the result is shown in Figure 2A. It is apparent that American researchers participate in more than half of the papers issued each year from 2007 to 2022. Although more and more countries have engaged in research activities in this field, the USA remains the most prominent country in terms of publication output.

2 https://bibliometric.com

Table 1 shows the status of the five countries with the most publications. It could be found that the majority of papers are issued by the top 5 countries reflecting the phenomenon of the Matthew Effect that does exist in this domain (19). America holds 67.7% of the total items (492/727). Furthermore, we analyzed collaboration patterns among countries/regions based on CiteSpace (Figure 2B). The value of BC reflects the significance of nodes in networks, which could assist to detect the crucial nodes. In general, "BC > 0.1" are viewed as the criterion to determine the importance, and nodes meeting the criterion would be shown with purple rings (17, 18). The USA plays a critical role in the cooperation network among countries/regions, with a centrality of up to 0.69. Canada (BC of 0.23) and England (BC of 0.11) are also influential in this field. Notably, Sweden holds the second highest centrality among countries (BC of 0.26) despite contributing only 30 papers. To ascertain Sweden's contribution to the development of the subject, we studied these 30 papers. We found that five articles had over 100 citations and 11 papers had more than or equal to 50 citations. In 2012, Bell et al. (20) found that APOE could regulate the activity of mural cells to control the integrity of the cerebrovascular system via the CypA-NFκB-MMP9 pathway, and CypA was a key target in the therapy of APOE-induced neurovascular impairment and neuronal dysfunction. By the time of our search, cited frequency of this document had reached 802 times. Winblad et al. (21) illustrated the economic burden, epidemiology, risk factors, pathogenic mechanisms, and prevention of Alzheimer's disease (AD) and other dementias (ADOD) in *Defeating Alzheimer's disease and other dementias: a priority for European science and society*. The researchers pointed out the issues existing in this field of ADOD in European society and put forward individual solutions to address each concern. This paper had been cited 882 times, implicating its significant contribution to the field. Another thing that needed to be focused on is the situation in China. China has observed a surge in post-TBI dementia research in recent years, with 77 publications, taking the second spot in number, but with a relatively low centrality (0.03). To examine our findings, we also visualized the collaboration among countries/regions with the help of a platform, "Bibliometric.com" (Figure 2C), which confirmed that the USA, Sweden, the UK, and Canada are actively engaging with other countries in this field.

As for institutions, we analyzed the co-authorship of organizations by VOSviewer, as shown in Figure 3A. Boston University, which has published 85 articles, possesses the most notable academic influence in this field with a total link strength

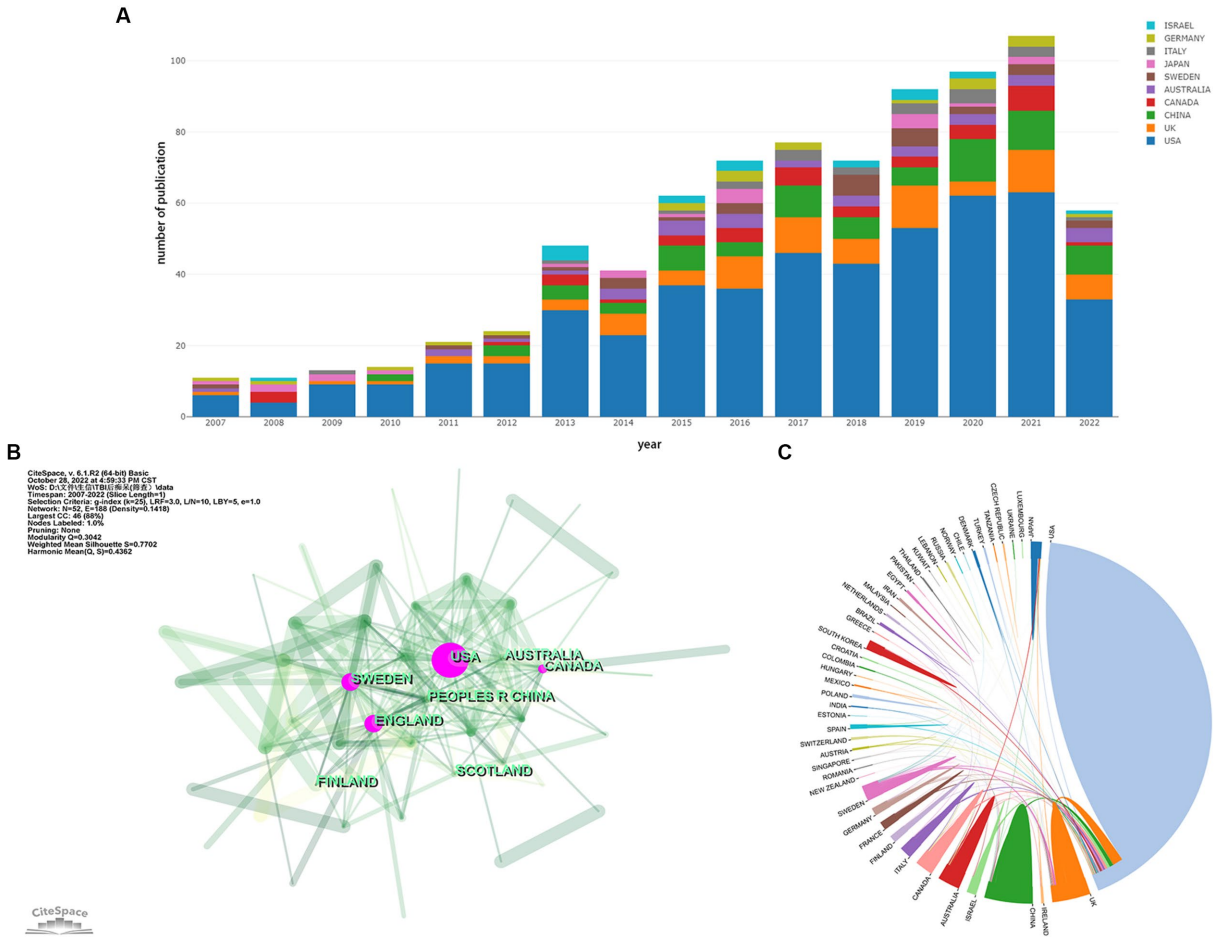

FIGURE 2
(A) Contribution of each country to the annual volume of publication. **(B)** Network map of countries/regions citation. **(C)** Visualization of international cooperation among countries/regions. The strength of cooperation is reflected in the thickness of the connection line. **(A,C)** are generated using https://bibliometric.com, while **(B)** is generated using CiteSpace.

TABLE 1 The top 5 countries in this field in terms of the number of publications.

Rank	Country	Documents	Citations	Average citations/ publications	Centrality
1	USA	492	23,798	48.4	0.69
3	CHINA	77	1,863	24.2	0.03
2	ENGLAND	61	3,379	55.4	0.23
4	CANADA	39	1,857	47.6	0.11
5	AUSTRALIA	34	1,573	46.3	0.01

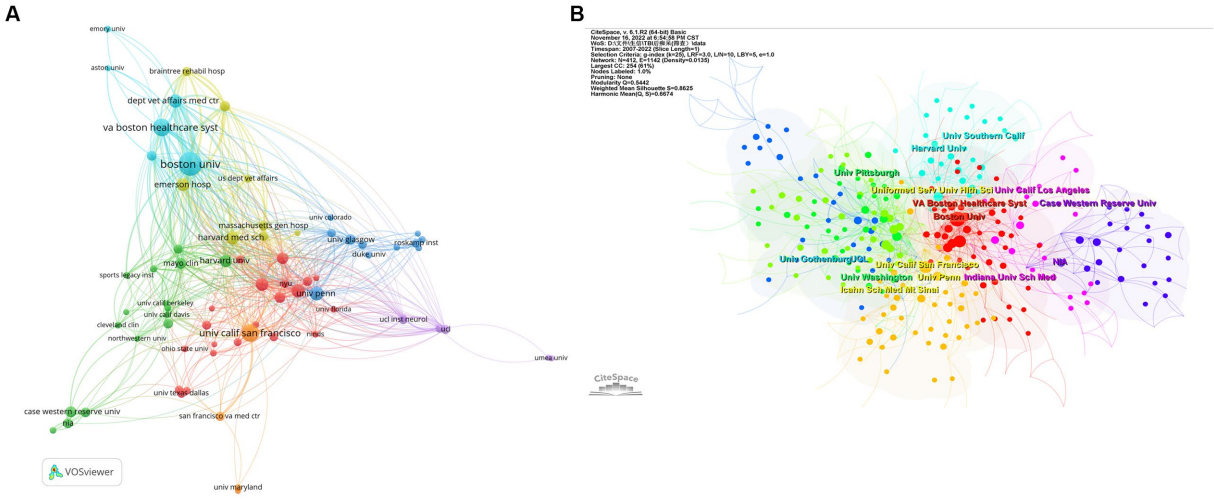

FIGURE 3
(A) Helicopter view of the co-authorship of the organizations. **(B)** Cluster view of co-authorship of organizations. **(A)** is generated using VOSviewer and **(B)** is generated using CiteSpace.

(TLS) of 383. Veterans Affairs Boston Healthcare System (TLS of 226), University of California San Francisco (TLS of 194), and Harvard Medical School (TLS of 192) also occupy crucial positions (Figure 3A). Table 2 shows the top 10 organizations with the largest number of articles. We also conducted a cluster analysis of institutions. The analysis identified nine clusters in total, of which seven are presented in Figure 3B. Some of the clusters had similar numbers of institutions. The red cluster, headed by Boston University and Harvard Medical School, consisted of 37 institutions, making it the largest cluster. And the orange cluster, headed by the University of California San Francisco and the Uniformed Services University of the Health Sciences, is the second-largest cluster with 29 institutes.

Bibliometric analysis of the journals

We conducted a statistical analysis of the periodicals in which the literature was published and found 262 journals in total. Table 3 shows the best 10 journals with the most papers in the field between 2007 and 2022. Notably, three journals had more than 25 articles: *Journal of Neurotrauma*, *Journal of Alzheimer's Disease*, and *Alzheimer's & Dementia*, with 60, 28, and 26 publications, respectively. Generally, the topics of the 10 journals involve Neuroscience, Clinical neurology, Rehabilitation, Pathology, and so on. Nine of the top 10 journals are specialized periodicals, except for *PLoS One*, which focuses on multidisciplinary science. *Alzheimer's & Dementia* has the highest impact factor (IF) of 16.7, making it a leading journal in the field. Among the top 10 journals, eight are located in Q1 and Q2, demonstrating the high quality of research output. *Journal of Neurotrauma* is the only peer-reviewed journal concentrating on traumatic brain and spinal cord injury, and it covers a broad series of research types from basic biology to clinical trials [Journal of Neurotrauma: (liebertpub.com)]. Figure 4A depicts the network analysis of the sources of articles retrieved. Among the sources, the *Journal of Neurotrauma* attracts the most articles and also has the best TLS value of 283, demonstrating its great reputation in the field. We could find an irregular distribution of the annual publication volume of the *Journal of Neurotrauma* from 2009 to 2022, according to Figure 4B. However, the journal's citation rate has shown consistent growth over the last decade or so.

TABLE 2 The top 10 institutions in terms of the number of publications.

Rank	Label	Total link strength	Documents	Citations
1	Boston University	383	85	6,749
2	Veterans Affairs Boston Healthcare System	226	50	3,831
3	University of California San Francisco	194	50	2,430
4	University of Pennsylvania	150	31	2,395
5	Harvard Medical School	192	29	690
6	Department of Veterans Affairs Medical Center	158	29	1,417
7	Uniformed Services University of the Health Sciences	159	28	1,284
8	Emerson Hospital	169	26	3,221
9	University of Washington	179	25	1,614
10	Harvard University	142	23	2,728

TABLE 3 The top 10 journals with the largest number of documents.

Rank	Source	Documents	Citations	IF (2021)	JCR (2021)	Research area
1	Journal of Neurotrauma	60	1,530	4.9	Q2	NEUROSCIENCES AND CLINICAL NEUROLOGY
2	Journal of Alzheimer's Disease	28	568	4.2	Q2	NEUROSCIENCES
3	Alzheimer's and Dementia	26	1,482	16.7	Q1	CLINICAL NEUROLOGY
4	Brain Injury	19	245	2.2	Q4	NEUROSCIENCES AND REHABILITATION
5	Plos One	16	643	3.8	Q2	MULTIDISCIPLINARY SCIENCES
6	Frontiers in Neurology	15	127	4.1	Q2	NEUROSCIENCES AND CLINICAL NEUROLOGY
7	Journal of Head Trauma Rehabilitation	14	287	3.1	Q3	REHABILITATION AND CLINICAL NEUROLOGY
8	Neurology	14	759	12.3	Q1	CLINICAL NEUROLOGY
9	Acta Neuropathologica	13	1,058	15.9	Q1	NEUROSCIENCES AND CLINICAL NEUROLOGY AND PATHOLOGY
10	Acta Neuropathologica Communications	13	300	7.6	Q1	NEUROSCIENCES

Bibliometric analysis of authors and co-cited authors

The study analyzed a total of 3,780 authors and 16,302 co-cited authors. We visualized the network analysis of the co-authorship of authors (Figure 5A) and the co-citation of cited authors (Figure 5B).

Table 4 represents the 10 most productive authors and the top 10 co-cited authors with the best citations. The top 3 productive authors are McKee AC, Stein TD, and Stern RA, with 46, 33, and 28 papers, respectively. Interestingly, McKee AC holds first place both in terms of the number of publications and citations, who has 46 items, 5,418 citations, and an average citation rate of 117.8 citations per publication,

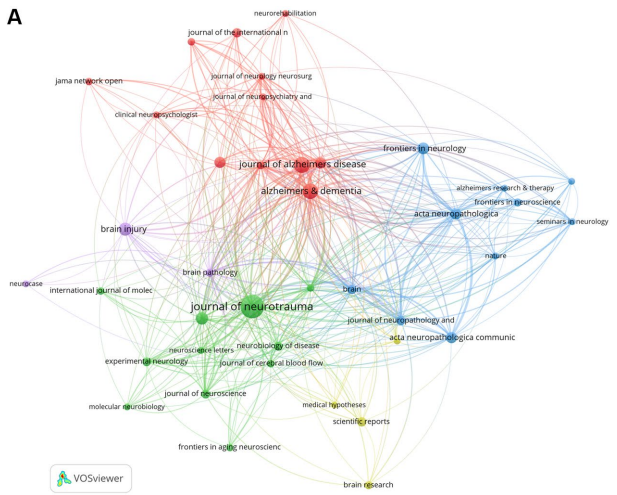

FIGURE 4
(A) Network analysis of the citation of journals. **(B)** The situation of publications and citations in the *Journal of Neurotrauma* from 2009 to 2022. **(A)** is generated using VOSviewer. **(B)** is created using Microsoft Excel 2019.

making her the most prolific author in this discipline. Except for Yaffe, nine out of the top 10 productive scholars take office at Boston University, indicating the significance of this institution in the field. As for the co-cited authors' network analysis, McKee AC, Johnson V, and Omalu B have the highest number of citations, and they also own the highest TLS scores, demonstrating their great contribution to this sector.

Network analysis of keywords

Figure 6A illustrates the evolution of keywords from 2007 to 2022. Notably, TBI and related terminology, Alzheimer's disease, and dementia were prominent almost throughout the analyzed period. Additionally, chronic traumatic encephalopathy (CTE), concussion, neurodegeneration, tau, and neuroinflammation gained increased attention during the last decade. The top 5 keywords with the highest frequency are traumatic brain injury, dementia, Alzheimer's disease, neurodegeneration, and tau-related terminology (*tau* and *tauopathy*) in 2022.

We generated a visual network of 85 frequently occurring keywords (frequency >16) across the 727 documents analyzed based on VOSviewer (Figure 6B). Through this, three distinct keyword clusters covering the years 2007 to 2022 were evident, and their specifics are shown as follows:

Cluster 1 encompasses a series of nouns outlining risk factors (e.g., *Concussion, Risk, Association, Risk-Factor, Encephalopathy, Age, Depression, Epidemiology, Mild Traumatic Brain Injury, Dysfunction, Prevalence, Older-Adult, Veterans, Impact, History, Population, Head Trauma, and Aging*), manifestation (e.g., *Cognitive Impairment, Encephalopathy, Memory, Depression, Impairment, Mild Cognitive Impairment, Cognition, Posttraumatic-Stress-Disorder, Dysfunction, Performance, and Cognitive Decline*), and therapy (e.g., *Rehabilitation, Recovery*).

Cluster 2 revolves around pathology and pathogenic mechanisms, covering a wide range of terms, such as *Alzheimer's Disease, Neurodegeneration, Mouse Model, Amyloid-Beta, Neuroinflammation, Inflammation, Expression, Axonal Injury, Protein, Amyloid Precursor Protein, Microglia, Beta, Oxidative Stress, Diffuse Axonal, Injury, Activation, Mechanism, Biomarker, Accumulation, Neuroprotection, Cerebrospinal-Fluid, Deposition, Apolipoprotein-E, Precursor Protein, Amyloid, and Deficit*. It also encompasses terminologies about research models, such as *Controlled Cortical Impact, Model, Transgenic Mice, Mice, Rat, and Closed-Head Injury*.

Cluster 3 is centered on CTE, including terminologies such as *Chronic Traumatic Encephalopathy*, *Dementia-Pugilistica*, and terms related to CTE and other neurodegenerative diseases, such as *Tau*, *Pathology*, *Disease*, *Brain-Injury*, *Diagnosis*, *Tauopathy*, *Neurofibrillary Tangle*, *Neuropathology*, *Injury*, *Frontotemporal Dementia*, *Neurodegenerative Disease*, *Parkinson's Disease*, *Amyotrophic-Lateral-Sclerosis*, *Frontotemporal Lobar Degeneration*, and *Degeneration*, as well as related issues, like *Football, National Institute*, and *Brain*.

Burst words are defined as keywords that emerge frequently within a given period, which imply research hot spots and development trends over time. Figure 6C shows the top 10 keywords with the strongest citation bursts.

The burst strength of the top 3 keywords, namely Aβ (amyloid β-protein), diagnosis, and amyloid precursor protein (APP), was found to be the highest. Specifically, Aβ, APP, and beta-secretase exhibited a citation burst between 2007 and 2015. Recently, scholars have placed greater value on diagnosis and outcome, making them the emerging focal points of the field. Other words that exhibited burst included apoe genotype (2007–2011), head injury (2013–2014), neurodegeneration (2016–2017), multiple sclerosis (2012–2016), and mice (2016–2018).

Bibliometric analysis of references

Figure 7A depicts the timeline view of references cited in these articles, and reveals the presence of 14 clusters. The earliest cluster, identified as Cluster #5 *neprilysin*, emerged in 2007 and vanished in 2014. Cluster #4 *long-term survival* and Cluster #6 *posttraumatic stress*

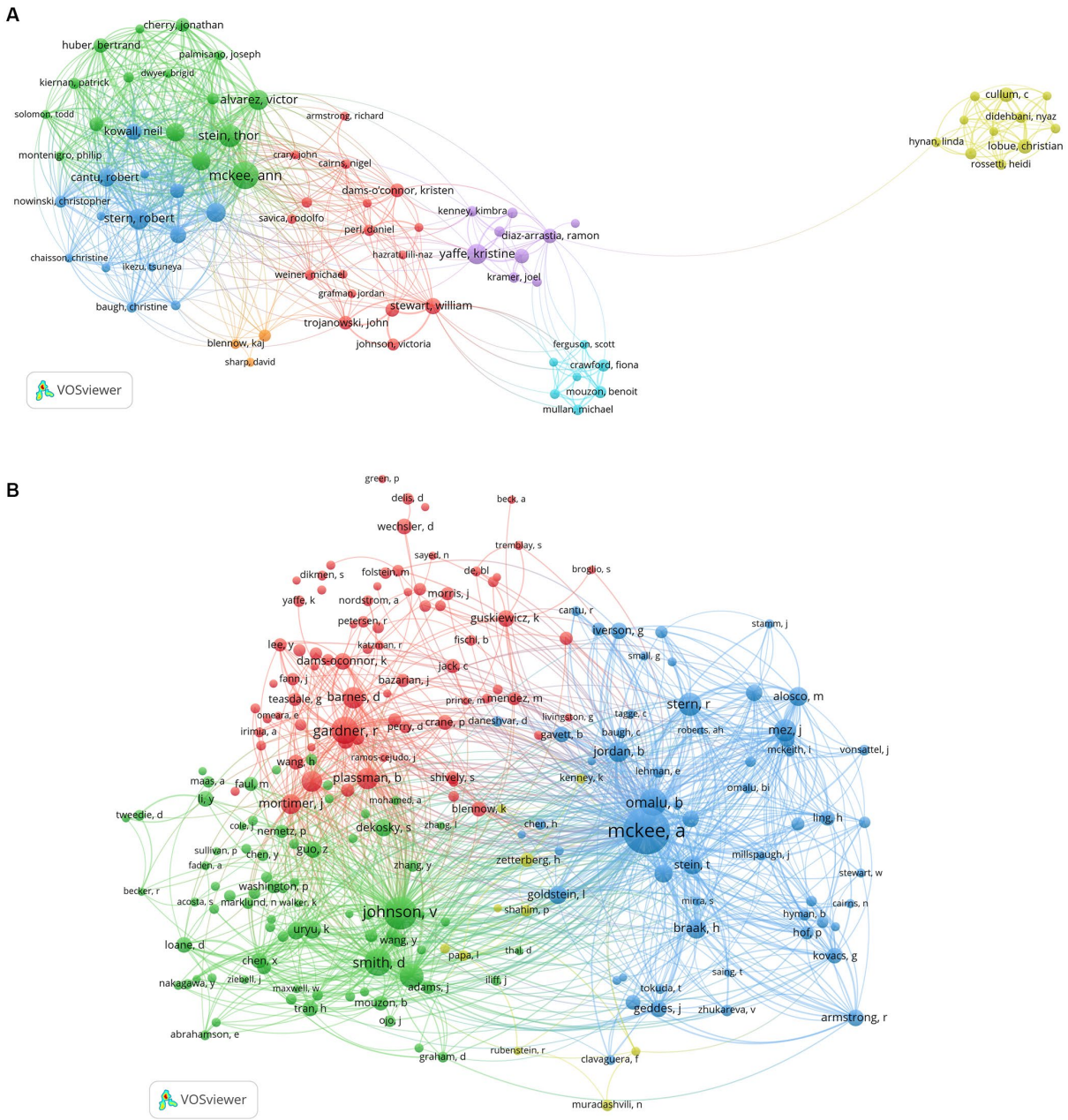

FIGURE 5
(A) The map of co-authorship of authors. **(B)** The map of co-citation of cited authors. **(A,B)** were performed on VOSviewer.

disorder represent the second and third earliest clusters, respectively. The largest one, Cluster #0 *chronic traumatic encephalopathy*, comprises 120 papers. And Cluster #13 *cardiovascular disease* is the most recent emergence, with its first appearance in 2021. References from Clusters #0, #3, and #13 are still active to this day.

The paper titled "*TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy*" (22) belongs to Cluster #4 and is notable with a high centrality of 0.13. It supplies the first evidence that repetitive traumatic brain injury (rTBIs) in contact sports might be associated with widespread TDP-43 proteinopathy and the onset and progression of motor neuron disease. Another bold piece of literature, belonging to Cluster #2, is "*The spectrum of disease in chronic traumatic encephalopathy*" (23), which has a centrality of 0.13 and the largest citation number of 103. In this paper, the researchers proposed a pathological staging of CTE and corresponding clinical manifestations based on evidence from postmortem brains and information from interviews with next of kin, which had greatly deepened our understanding of this disease.

We observed that the distribution of literature was imbalanced, with more than half of the references originating from the first four clusters (Figure 7A). Upon examining the citation trends over the years (as shown in Supplementary Figure S3), we made an interesting discovery. From 2007 to 2012, most of the cited references were concentrated in Clusters #4, #5, and #6. On the other hand, between

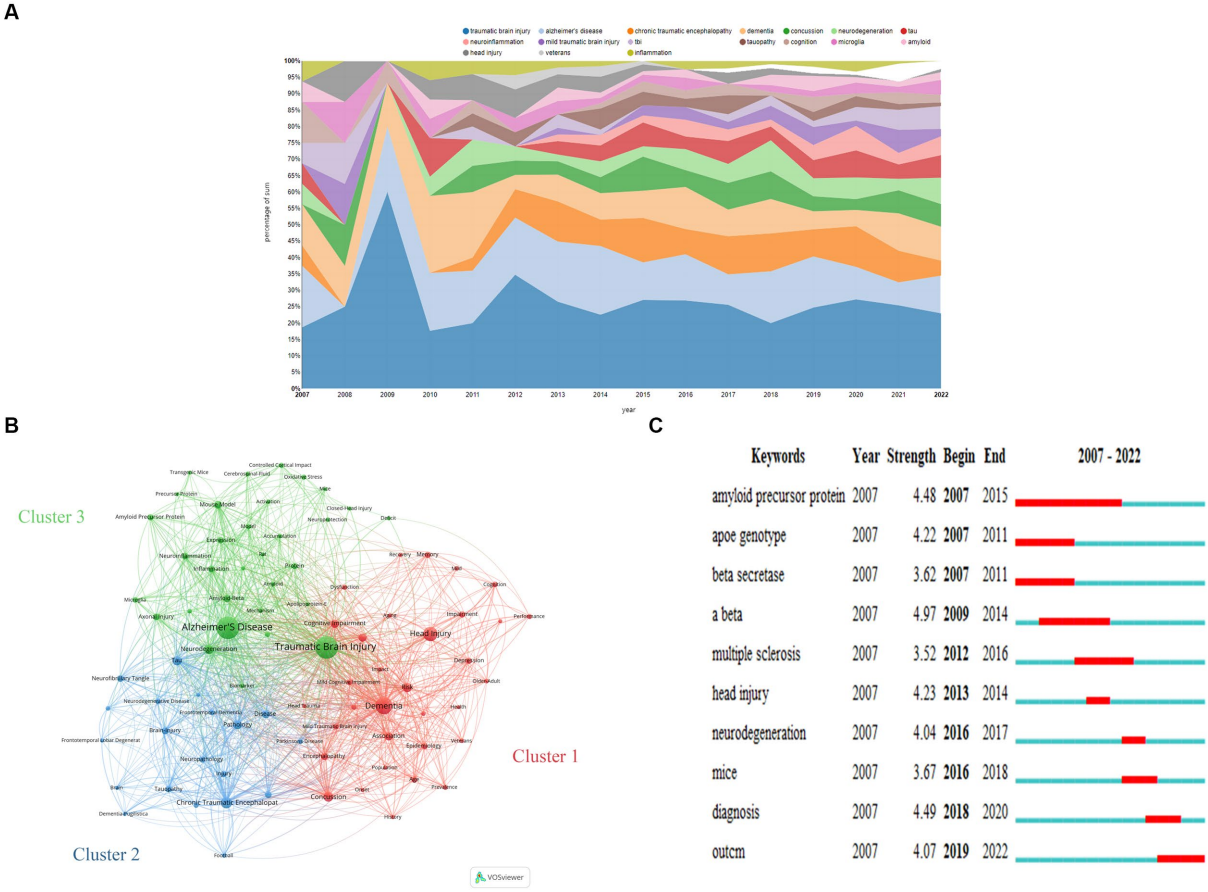

FIGURE 6
(A) Transition of keywords over the 15years analyzed. **(B)** Network Visualization of keywords with a frequency of more than 16 in this field from 2007 to 2020 based on VOSviewer. **(C)** The top 10 keywords with the strongest citation bursts based on CiteSpace. **(A)** was obtained from https://bibliometric.com.

TABLE 4 The most productive authors in this field and the top 10 co-cited authors with the highest citations.

Rank	Author	Documents	Citations	Average citations/ publication	Co-cited author	Citations	Total link strength
1	Mckee, AC	46	5,418	117.8	Mckee, AC	629	10,550
2	Stein, TD	33	3,377	102.3	Johnson, V	306	5,180
3	Stern, RA	28	3,691	131.8	Omalu, B	205	4,039
4	Yaffe, K	26	1,517	58.3	Gardner, R	204	3,063
5	Alvarez, VE	25	3,037	121.5	Smith, DH	204	3,833
6	Tripodis, Y	24	1,578	65.8	Roberts, G	159	3,045
7	Alosco, ML	21	752	35.8	Stern, RA	147	2,786
8	Mez, J	21	746	35.5	Mez, J	144	2,716
9	Cantu, R	20	2,889	144.5	Plassman, B	130	2,297
10	Kowall, N	16	2,458	153.6	Barnes, DE	128	1,765

2013 and 2017, studies belonging to various clusters were cited. After 2018, the majority of citations were derived from the first four clusters (Clusters #0, #1, #2, and #3). Therefore, we focused our attention on Clusters #0, #1, #2, and #3 (Figure 7B) to track the kernel of the discipline at the moment. The labels of the 4 clusters are *chronic traumatic encephalopathy*, *age of onset*, *tauopathy*, and *cognitive decline*, respectively. We checked the high-frequency words in each cluster to investigate potential research frontiers (Table 5). Our findings reveal

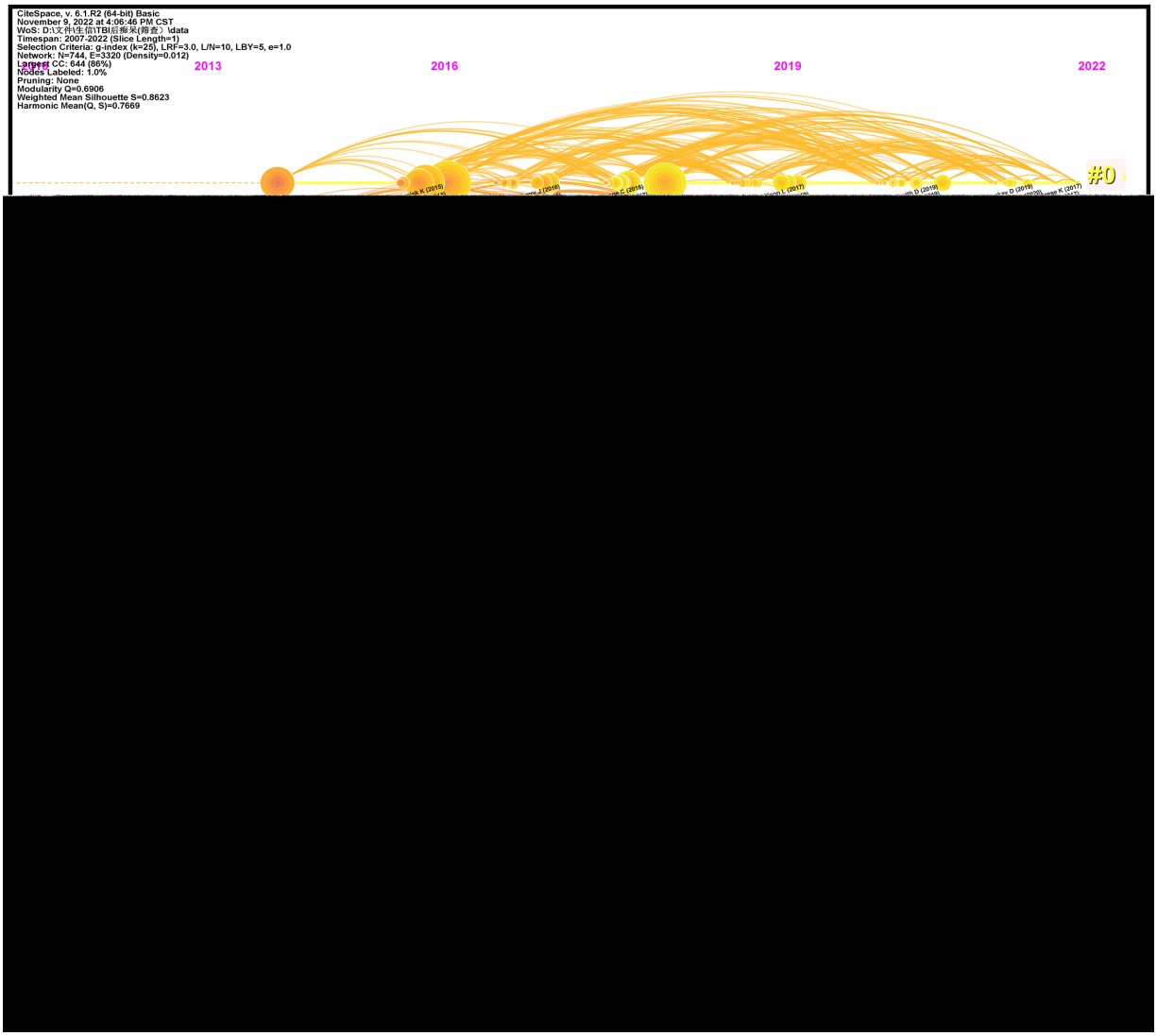

FIGURE 7
The timeline view of references. **(A)** Overview of 14 clusters. **(B)** Specifics of Clusters #0-#3 (dashed frame in **A**). The figure is obtained from CiteSpace.

that common words, for example, *CTE*, *TBI-related*, *AD*, *tau-related*, *football*, and *cognition-related*, appear in most clusters if not all. These words mirror the shared research directions across the four classifications.

Additionally, exclusive terminologies were identified for each cluster. Cluster #0 exhibits unique content such as *Diagnostic validity*, *rater reliability*, *amyloid beta peptides*, *numerical data*, *proteome*, and *extracellular vesicles*. The terms specific to Cluster #1 include *apoe4*, *cortical thickness*, *age of onset*, and *controlled cortical impact*. Cluster #2 focuses on exclusive words such as *neurofibrillary tangles*, *principal components analysis*, *astrocytic tangles*, and *monoacylglycerol lipase*, while Cluster #3 incorporates terminologies such as *repetitive head impacts*, *animal models*, *Parkinson's disease*, *amyotrophic lateral sclerosis*, *seizure disorder*, and *axonal injury*.

We also explored the top articles in the four clusters. Table 6 shows the top 5 papers with the most citations in four clusters. The specifics of the top 5 papers in each cluster are shown in Table 7.

Discussion

Over the past 15 years, there has been a consistent increase in publications and citations pertaining to studies on post-TBI dementia. The bibliometric analysis allows for the visualization of several quantitative indicators and facilitates a more intuitive comprehension of the literature as compared to systematic reviews (17). In this study, we employed bibliometric analysis to examine the discipline of post-TBI dementia from various perspectives, including authors, journals, countries, institutions, keywords, and references, to gain a comprehensive understanding of research trends in this field globally and identify potential avenues for future development.

General information

In this study, a total of 727 articles, between 2007 and 2022, from WOSCC were analyzed, which came from 1,126 institutions and 52

TABLE 5 Sketch of the first 4 clusters of references.

Cluster	keywords	Size	Span
#0	Chronic traumatic encephalopathy; traumatic brain injury; executive function; diagnostic validity; rater reliability | Alzheimer's disease; amyloid beta peptides; microtubule-associated proteins; tau proteins; numerical data; chronic traumatic encephalopathy (22.53); football (13.29); proteome (10.33); extracellular vesicles (10.33); neurodegenerative disease (9.84)	120	Date from 2014
#1	Traumatic brain injury; Alzheimer's disease; cognitive decline; normal cognition; risk factor | chronic traumatic encephalopathy; neurodegenerative disorders; apoe4; cortical thickness; neurodegeneration; age of onset (12.27); tauopathy (9.78); chronic traumatic encephalopathy (9.18); football (7.3); controlled cortical impact (6.12)	105	2013 ~ 2020
#2	Chronic traumatic encephalopathy; neurofibrillary tangles; principal components analysis; astrocytic tangles; monoacylglycerol lipase | traumatic brain injury; Alzheimer's disease; risk factors; head injury; memory loss; chronic traumatic encephalopathy (15.71); tauopathy (9.24); concussion (8.71); neurodegenerative disorders (6.41); brain trauma (4.9)	102	2011 ~ 2018
#3	Traumatic brain injury; chronic traumatic encephalopathy; repetitive head impacts; animal models; mild behavioral impairment | Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; soccer ball; seizure disorder; chronic traumatic encephalopathy (13.28); cognitive decline (8.92); traumatic brain injury (5.77); football (5.07); axonal injury (4.39)	82	Date from 2016

countries, authored by 3,780 authors, issued in 262 journals, and cited 25,713 references from 3,921 journals. Based on our study, it is evident that the discipline of post-TBI dementia has seen a steady development over the past 15 years, with increasing international participation. The United States, with a centrality of 0.69, is, without doubt, the most influential country in this field, contributing 67.7% of openly published papers. Moreover, all 10 top institutions are located in the USA, reinforcing America's dominance as a leader in this domain (Table 2). Our findings also demonstrate that Chinese scholars have shown considerable interest in the subject of post-TBI dementia, with their number of research publications ranking second. Nevertheless, despite China's conspicuous number of publications, its centrality ranking was relatively low indeed, indicating the need for strengthened academic cooperation and influence. It is imperative for China to conduct more high-quality research to reinforce its standing in this field. Our study also highlights the noteworthy research capabilities and robust collaboration of Sweden, which, despite having published only 30 papers, exhibits the second-highest centrality in the field.

Among the 10 top organizations, Boston University played a pivotal role in the study of post-TBI dementia, manifesting the highest number of articles and the highest TLS of 383. Other institutions, like the University of California San Francisco and Harvard University, also emerged as significant contributors to the development of the subject. In contrast to the country analysis, our network analysis showed no dominant institute, and focusing on different research directions, institutes form alliances with each other, leading to the formation of various clusters throughout the field. Almost all clusters of institutions were headed by American institutes, further suggesting that America dominates the field. Grasping the information about the authors is conducive to answering a significant question: Who are the pivotal authors? Our analysis demonstrates that the most well-known author in the area is McKee AC, with 5,418 citations, followed by Stern RA, Stein TD, Alvarez VE, Tripodis Y, and Yaffe K, all of whom are eminent scientists known for their remarkable productivity. McKee AC is no doubt the leading scientist in this domain, who has focused on AD and CTE constantly. She has an incredible interest in the pathology of neurodegenerative diseases, the action of tau, axon impairment, trauma, and vascular dysfunction. She has also conducted extensive researches on mild TBI (mTBI), induced by contact sports and military services, as well as its long-term effects [Ann C. McKee | Graduate Medical Sciences (bu.edu)]. She has contributed to over 70% of CTE cases reported to date [Ann McKee, MD | CTE Center (bu.edu)]. Of the top 10 productive authors, 5 are affiliated with Boston University, which demonstrates the contribution and influence of this institute. Analysis of journals could assist us to determine the distribution of literature across journals, identify the "core periodicals," and provide some guidelines for manuscript submission. *Journal of Neurotrauma* ranks first in terms of the number of publications, followed by *Journal of Alzheimer's Disease* and *Alzheimer's & Dementia*.

Hot spots and Frontiers

Keywords represent the core of a paper, assisting readers to understand quickly what the papers are about and which domain the articles pertain to. The transition of keywords could embody the development of subjects. Our analysis revealed that during the past decade, several terms, including CTE, concussion, neurodegeneration, tau, and neuroinflammation, had been frequently referenced in the literature. Additionally, TBI and TBI-related terminologies, as well as AD and dementia, have been identified as current hot spots in this field. Furthermore, co-occurrence analysis of keywords enables the identification of research frontiers. We observed three distinct clusters related to post-TBI dementia through a keywords network analysis, namely: (1) terms about risk factors, manifestation, and therapy; (2) terminologies relevant to pathology, pathogenic mechanisms, and models; and (3) CTE-related terminologies.

Mainstream viewpoints to date support TBI as a risk factor for dementia (4, 6, 10). Stopa et al. (2) conducted a retrospective cohort study with a follow-up period of greater than 10 years and found a positive relationship between TBI and dementia. Another cohort study held by Osler et al. (3) also supported this kind of association. Many meta-analyses had also drawn conclusions agreeing with the

TABLE 6 The top 5 papers from the first 4 clusters, respectively.

Cluster	Rank	Title	Count	References	Journal	Year of publication	Year of the first citation	Year of the last citation	Centrality
0	1	The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy	82	Mckee et al. (24)	ACTA NEUROPATHOL	2016	2016	2021	0.09
	2	Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football	67	Mez et al. (25)	JAMA-JAM MED ASSOC	2017	2018	2022	0.07
	3	Beta-amyloid deposition in chronic traumatic encephalopathy	47	Stein et al. (26)	ACTA NEUROPATHOL	2015	2016	2020	0.04
	4	Clinical presentation of chronic traumatic encephalopathy	38	Stern et al. (27)	NEUROLOGY	2013	2014	2018	0.05
	5	Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank	37	Bieniek et al. (28)	ACTA NEUROPATHOL	2015	2016	2020	0.03
1	1	Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings	43	Crane et al. (29)	JAMA NEUROL	2016	2017	2021	0.08
	2	Dementia risk after traumatic brain injury vs. nonbrain trauma: the role of age and severity	27	Gardner et al. (30)	JAMA NEUROL	2014	2015	2019	0.04
	3	Chronic neuropathologies of single and repetitive TBI: substrates of dementia?	29	Smith et al. (31)	NAT REV NEUROL	2013	2014	2018	0.05
	4	Traumatic brain injury and risk of dementia in older veterans	38	Barnes et al. (32)	NEUROLOGY	2014	2015	2019	0.07
	5	Traumatic brain injury and young onset dementia: a nationwide cohort study	24	Nordstrom et al. (33)	ANN NEUROL	2014	2015	2019	0.03

(Continued)

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TABLE 6 (Continued)

Cluster	Rank	Title	Count	References	Journal	Year of publication	Year of the first citation	Year of the last citation	Centrality
2	1	The spectrum of disease in chronic traumatic encephalopathy	103	Mckee et al. (23)	BRAIN	2013	2013	2018	0.13
	2	Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model	42	Goldstein et al. (34)	SCI TRANSL MED	2012	2013	2017	0.06
	3	The neuropathology of sport	35	Mckee et al. (35)	ACTA NEUROPATHOL	2014	2015	2019	0.04
	4	The neuropathology of chronic traumatic encephalopathy	30	Mckee et al. (36)	BRAIN PATHOL	2015	2015	2020	0.01
	5	Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome	28	Montenigro et al. (37)	ALZHEIMERS RES THER	2014	2015	2019	0.04
3	1	Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans	49	Barnes et al. (38)	JAMA NEUROL	2018	2019	2022	0.03
	2	Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study	36	Fann et al. (39)	LANCET PSYCHIAT	2018	2019	2022	0.03
	3	Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis	29	Perry et al. (5)	J NEUROSURG	2016	2017	2021	0.06
	4	Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study	26	Nordstrom et al. (40)	PLOS MED	2018	2019	2022	0.01
	5	Traumatic Brain Injury and Alzheimer's Disease: The Cerebrovascular Link	23	Ramos-Cejudo et al. (41)	EBIOMEDICINE	2018	2019	2022	0.01

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TABLE 7 The profile of the top 5 papers from the first 4 clusters.

Cluster	Rank	Title	Profile
0	1	The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy	Defined the neuropathological criteria for the diagnosis of CTE
	2	Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football	Postmortem of brain of former American football players suggesting the relationship between CTE and history of football-playing
	3	Beta-amyloid deposition in chronic traumatic encephalopathy	(1) The deposition of Aβ was altered and accelerated in patient of CTE compared with normal aging people (2) Aβ was related to severity of CTE independent of age
	4	Clinical presentation of chronic traumatic encephalopathy	Introduced two major kinds of manifestation of CTE, that is "behavior/mood variant" and "cognitive variant"
	5	Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank	(1) Reported a few cases with concomitant CTE pathology and neurodegenerative diseases (2) Found CTE pathology was only detected in those people with the history of contact sports
1	1	Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings	(1) Studied the relationship between TBI with loss of consciousness (LOS) and neurodegenerative diseases as well as neuropathological alternation (2) Found TBI with LOS had something to do with increased risk for Lewy body accumulation, PD, progression of parkinsonian signs and microinfarcts, but might have nothing to do with dementia, AD, neurofibrillary tangles and neuritic plaques
	2	Dementia risk after traumatic brain injury vs. nonbrain trauma: the role of age and severity	(1) Investigated the link between TBI and dementia (2) Demonstrated that younger adults were more tolerated with mild TBI than older people in term of onset of dementia
	3	Chronic neuropathologies of single and repetitive TBI: substrates of dementia?	A review about chronic neuropathological changes post TBI
	4	Traumatic brain injury and risk of dementia in older veterans	Identified positive relationship between TBI and development of long-term dementia in older veterans
	5	Traumatic brain injury and young onset dementia: a nationwide cohort study	Proposed that TBI of different severity might increase risk of young onset dementia (YOD) of non-AD forms
2	1	The spectrum of disease in chronic traumatic encephalopathy	Proposed the pathological staging of CTE and corresponding clinic manifestation based on evidences from postmortem brain and information from interviews with next of kin
	2	Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model	(1) Discovered the existence of CTE pathology in postmortem brains from blast-exposed veterans (2) Introduced a blast neurotrauma mouse model
	3	The neuropathology of sport	A review mentioning the sport-related adverse neuropathological changes including CTE
	4	The neuropathology of chronic traumatic encephalopathy	A review about CTE
	5	Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome	(1) Reviewed the clinical manifestation of CTE (2) Suggested diagnostic criteria for research of CTE and related disorders

(Continued)

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TABLE 7 (Continued)

Cluster	Rank	Title	Profile
3	1	Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans	A cohort study investigating the association of different severity of TBI, especially mild TBI with or without LOS, with dementia
	2	Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study	(1) A cohort study exploring the relationship between TBI and dementia (2) Found TBI could increase the risk of dementia in a seemingly dose-dependent way, that is the risk of dementia raise with augmentation of the number of TBI
	3	Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis	(1) Supported that there was a strong relationship between prior TBI and long-term neurological and psychiatric diseases (2) Proclaimed that there was no evidence that more TBI could induce higher risk of disease
	4	Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study	(1) Supported the kind of "dose-dependent" relationship, found that more severe and multiple TBI could induced higher risk of dementia diagnosis (2) Noticed risk decreased over time post TBI, although it was still notable even though more than 30 years after assault
	5	Traumatic Brain Injury and Alzheimer's Disease: The Cerebrovascular Link	A review focusing on cerebrovascular connection between TBI and AD

above studies (4, 5). However controversy still existed (7). It might be reasonable to say that not all TBIs are associated with an increased risk of developing dementia. One important consideration when planning research on post-TBI dementia is the variability of injury parameters [e.g. frequency (5)severity (2, 4)] and patient states [e.g. age (2, 4) and genotype (42)] across different settings. Concerning treatment, statins might become a potential medication for TBI patients. Redelmeier et al. (43) found that statins could decrease the risk of dementia in patients with a concussion. Atorvastatin seems to improve the prognosis of mild and moderate TBI patients (44). Li et al. (45) found that the combined use of angiotensin-converting enzyme inhibitors (ACEI) and statins could reduce the risk of possible AD in TBI patients. Further large-scale clinical trials should be initiated to authenticate the findings and their generalizability

Despite the growing interest in academia, the underlying mechanisms of post-TBI dementia remain unclear. The hypotheses in this regard are multi-factorial, comprised of deposition of pathological proteins, cognition reserve, chronic inflammation, chronic activation of microglia, degeneration of synaptic junctions induced by the alteration of protein degradation, excitotoxicity, overload of calcium ions, dysfunction of the mitochondrion, etc. (46, 47). Various TBI models have been employed in related studies, namely, shock wave tubes, Controlled Cortical Injury (CCI), Weight Drop Injury (WDI), and Fluid Percussion Injury (FPI), among others. CCI is used for focal injuries, while shock wave tubes are for diffuse injuries. WDI could cause either focal or diffuse injuries, depending on the experimental parameters chosen. Generally, mild WDI is relevant for diffuse injuries, while severe WDI could cause focal contusions. On the other hand, FPI could produce diffuse or mixed injury by setting different impulse pressures in experiments. FPI has been identified as the most dependable, repeatable, and practical model for blast injury (48). Furthermore, cognition impairment existing in open TBI is different from that in closed head injury even if the physiological condition is kept constant (48). Thus, the choice of appropriate models to mimic the injuries of reality is essential for research.

The contributions of many parties have led to CTE becoming a focal point in the field of neurotrauma. In 1928, Martland (49) introduced the disease of CTE to describe neuropsychiatric manifestations in pugilists – known as "punch drunk" at that time. This syndrome was later referred to as "dementia pugilistica" and is currently recognized as CTE (50). Nowadays, the application scope of the terminology is not limited to boxing but to extensive settings, such as football players (51). Omalu et al. (51) reported a case of CTE in a former National Football League player, arousing both academic and public concern about the neurological sequelae of contact sports. The film "*Concussion*," adapted according to the experiences of Bennet Omalu, raised public awareness of this kind of neurodegenerative disease. The discovery of CTE has affected the real world deeply, raising emphasis on rTBIs in scientific, sports, and public contexts. The studies on CTE were also infested with controversy, as was the case with TBI (50), and further studies are necessary to fully understand the disease.

In co-citation and co-cited analyses, we may overlook the newly published papers that have not got enough attention. The detection of burst words is a way to solve the problem (15). Figure 6C illustrates that Aβ, APP, and β-secretase experienced a burst in popularity, between 2007 and 2015. Aβ, a kind of polypeptide of 38–43 amino acids, is formed by the decomposition of APP with the help of β-secretase and γ-secretase (47). Aβ has attracted strong interest from

neuroscientists due to its visible manifestation in the pathology and pathogeny of AD. There seems to be a linkage between TBI and Aβ. Some scholars had found that TBI might increase the level of deposition of Aβ in the global, frontal cortex, and posterior cingulum (52). Further studies are needed to fully understand the role of Aβ in post-TBI dementia. In recent years, attention among researchers has gradually shifted to the prognosis and diagnosis of the disease. As for prognosis, numerous epidemiological studies are springing up, aiming to reveal cognition alteration and the onset of dementia following TBI (3, 8, 9). In respect of diagnosis, studies about biomarkers have become a trending topic. Except for Aβ, tau, which could regulate the elongation and stability of microtubes, has received great attention. The function of tau depends on its level of phosphorylation. And TBI could disturb the stability of microtubes and the activity of the nervous system by changing the level of phosphorylation of tau (53). Moreover, as a characteristic of the pathology of CTE, tau shows an immense practical perspective for diagnosis (24). Other potential diagnosed indicators include α-synuclein, TDP-43 (TAR DNA binding protein-43), the light chain of neurofilament, and cavum septum pellucidum (CSP) (54, 55). In addition, the keywords "multiple sclerosis" and "mice" also demonstrated a burst phenomenon (Figure 6C). The prominence of multiple sclerosis suggested that multiple sclerosis might be one of the potential complications post-TBI and received great interest from scholars worldwide. As was common in life science research, mice were frequently used as animal models in the research field of post-TBI dementia, having strongly contributed to the development of this discipline. Notably, the appearance and extinction of burst words may not always accurately mirror the development of a subject. For instance, the word "Apo E" (Apolipoprotein E) burst from 2007 to 2011 but was not detected after 2011, as shown in Figure 6C. Nevertheless, plenty of studies about Apo E sprout continuously, appealing to scientists in many fields. Apo E, which plays a pivotal role in the transportation of lipids in the central nervous system, has three types of alleles that correspond to encoding three kinds of proteins: E2, E3, and E4 (56). Especially, E4 is viewed as a risk factor for poor prognosis after TBI and contact sports (42), which might be a key target of post-TBI dementia. Therefore, the interpretation of the developmental trend of subjects is the result of an integrated analysis of an assortment of data.

References, cited by periodicals, constitute the research base of the subjects studied. The analysis of references (research bases) cited in research articles could reveal the evolution of research frontiers and the changes in disciplinary trends. The Cluster #5 Neprilysin was the earliest cluster. Neprilysin (NEP) is considered an ectoenzyme that could catalyze the proteolysis of several substrates, for example, enkephalins and tachykinins. Moreover, NEP might be a potential target of AD therapy, which was thought to be one of the primary amyloid-degrading enzymes. Many studies have revealed the role of NEP in cognitive function. Reduced levels of NEP expression and activity were identified in the cortex of elderly AD patients. Upregulation of NEP expression might alleviate the AD-like symptom (57). However, Maigler et al. (58) found that NEP or NEP2 deficiency seemed not to aggravate impairments in spatial learning or memory post-TBI. In some cases, NEP (NEP or NEP2) deficiency may have actually been protective. This finding contradicts previous research on the role of NEP in cognitive function and highlights the need for further investigation to reconcile this controversy.

Our analysis of the timeline view of cited references shows that the first 4 clusters were the primary sources of citations (Figure 7A). Furthermore, our examination of the evolution of references over time revealed a notable pattern (Supplementary Figure S3). From 2007 to 2012, the majority of references were clustered within three groups (Cluster #4, #5, and #6). However, from 2013 to 2017, research within this timeframe was widely dispersed and lacked a concentrated focus on any particular cluster. Beginning in 2018, a discernible trend toward established research directions in the area of post-TBI dementia emerged, characterized by Clusters #0, #1, #2, and #3. Overall, these findings reflect the natural process of scientific progress. As time went on, the research in this subject evolved and developed, moving from its early stages where knowledge was limited and only very limited domains can be explored, to a more advanced and complex understanding of the topic. Along the way, researches made "new" discoveries, which resulted in the exploration of different domains within the field. This led to a proliferation of studies across the entire spectrum of the discipline, as scientists chased the research frontiers. Eventually, with the growth of knowledge, a credible and promising mainline emerged, attracting the attention of the majority of scholars in the field.

Therefore, our focus shifted to the four clusters (Figure 7B). It seems that though these clusters share several common research themes, each also cultivates unique directions of inquiry. For instance, Cluster #0 appears to prioritize the diagnosis of the disease, while Cluster #1 centered on investigating the disease's associated risk factors. In contrast, Cluster #2 examines pathology and pathophysiology within the context of the disease, and Cluster #3 might be earmarked for studies exploring the associations between TBI and various other diseases. To substantiate our hypothesis, we conducted a thorough examination of the influential articles in each cluster. We find a striking resemblance and considerate overlap in the first 4 clusters despite being separate clusters according to the CiteSpace algorithm. These clusters predominantly revolve around the correlation between TBI and dementia-related changes, along with knowledge concerning CTE, thereby indicating that epidemiological studies about causality are influential and highly sought after in this field, alongside studies concerning CTE. And the pathology of TBI and CTE is also a critical topic in this field. The aforementioned observations lend further support to the findings obtained from the cluster analysis of keywords.

It is worth noting that Cluster #13 *cardiovascular disease* appears to be a relatively new area of research, which may suggest a future research subfield. Eric Nyam et al. (59) found that TBI patients had increased risks of the onset of "major cardiovascular and cerebrovascular events" (MACCE), with the highest incidences within the first year following the diagnosis of TBI. Kumar et al. (60) found that hypertensive disease was one of the most prevalent comorbid conditions among TBI patients 55 years of age and older. Hammond et al. (61) discovered that hypertension and high blood cholesterol were prevalent comorbidities diagnosed synchronously with or after TBI, especially among people older than 50 years at the end of the follow-up, despite the possibility that the incidence of these two comorbidities seemed to be more relevant to aging than TBI. Combined with the fact that traumatic microvascular injury was considered one of the potential pathogenic mechanisms of chronic sequelae post-TBI (1), research on the cardiovascular and cerebrovascular alterations after TBI might become a future hotspot in this discipline.

When we searched papers on the bibliometrics of post-TBI dementia, we noticed an article, *Bibliometric Analysis of Chronic Traumatic Encephalopathy Research from 1999 to 2019* (62), which

shares similarities with our own conclusion. For example, the study found that the USA had the highest number of CTE-related publications, with nine of the top 10 institutions located in America, notably Boston University with the highest number of publications, which is not surprising given its focus on CTE. Cognition impairment is a common and notable manifestation of CTE (27), which could occur in TBI patients of diverse occupations, for example, boxers (49), football players (51, 63), and military servicemen (23). Some CTE patients suffer from cognition dysfunction as the initial manifestation (27). As our study focuses on post-TBI dementia, we cannot overlook the research area of CTE, and studies on changes in cognitive function in CTE should be included in our retrieval results. Our findings demonstrate that research about CTE represents a substantial proportion of the discipline of post-TBI dementia. CTE has emerged as a significant research direction in the field of post-TBI dementia.

Current controversies and prospects

The consensus amongst the majority of scholars is that TBI is a significant risk factor for dementia. However, generous studies suggest that not all TBIs are likely to be associated with an increased risk of developing dementia. Grasset et al. (8) did not establish such a long-term link between TBI with loss of consciousness (LOC) and dementia or memory decline. Nguyen et al. (9) also did not discover a significant correlation between remote TBI with LOC and the onset of Dementia with Lewy bodies (DLB). And Plassman et al. (10) thought that TBI was associated with non-Alzheimer's disease dementia but not AD. The relationship between TBI and dementia has gained considerable attention among scholars in this area, and a definite causality between the previous history of TBI and dementia onset has not been established (7). Therefore, future research is warranted to gain an in-depth understanding of post-TBI dementia. Several researchers (4, 38, 64) observed that patients with a history of moderate or severe TBI had a greater risk of developing dementia compared with those with mTBI, which seemed to suggest a dose-dependent relationship between TBI severity and subsequent dementia risk. However, this perspective has been challenged. Stopa et al. (2) proposed that the risk of dementia after mTBI was greater than that of moderate and severe TBI. This inconsistency of findings might be due to the distinctive pathogenic mechanisms by which TBIs of diverse severity participate in the progression of dementia. MTBI without LOC might induce an increased risk of dementia primarily via accelerating brain atrophy, whereas moderate to severe TBI affects more baldly the deposit of Aβ and tau (38). Repetitive TBIs could exacerbate the damage and lead to worse outcomes (1, 65), supporting the aforementioned dose-dependent relationship. However, as with the findings on the implications of the severity of TBI, controversy exists surrounding the frequency of TBI. Perry et al. (5) proposed that repeated TBIs did not result in a significantly increased risk of dementia compared to a single TBI. Godbolt et al. (66) pointed out that neither single nor repeated mTBIs induced a significantly raised risk of dementia. In sum, the nature of TBI could evidently affect its prognosis. It is necessary to carry out additional studies that control for variables and investigate the relationship between TBIs with varying characteristics and dementia. Moreover, it is significant to validate this dose-dependent relationship for a comprehensive understanding of the correlation between TBI and dementia, which would guide clinical decision-making.

CTE is a distinctive neurodegenerative disease characterized by a spectrum of distinguishing pathological features like the unique configuration or distribution of tauopathy, which are different from those that existed in aging, AD, or any other tauopathy (23, 67). Age-related tau astrogliopathy (ARTAG), a form of astrocytic phosphorylated tau pathology, is an age-related alteration that is common in CTE. A few researchers might have mistakenly interpreted ARTAG as a diagnostic pathology of CTE, leading to disputed findings (67). CTE has gradually received much attention for its strong association with TBI, especially rTBIs (23, 54, 67). Nevertheless, a conclusive causal relationship between rTBIs and CTE has not been established yet. The latest article by McKee et al. (67) on neuropathological diagnostic criteria for CTE did support such a causality despite the lack of definitive evidence. Currently, the diagnosis of CTE relies on its specific neuropathological alterations (24, 68), which makes it challenging to diagnose patients with CTE definitely during their lifetime. There is a need for diagnostic criteria for CTE that are more applicable to clinical work. In addition, demonstrating such causality could be difficult due to possible selection bias, limitations of research types (e.g., cross-sectional studies and case reports), and other factors from previous studies. Furthermore, accurately quantifying the lifetime TBI exposure, which is significant and necessary to clarify the unknowns in the field of post-TBI dementia, could also be a huge issue (7, 69). Prospective and longitudinal studies of individuals with a hazard of developing CTE are necessary to overcome these challenges. This can be achieved by incorporating clinical injury exposure metrics, collected through wearable measurement devices, as well as evolving fluid and neuroimaging biomarkers (67, 69).

As previously mentioned, TBI could increase the risk of developing AD, VD, PD, and MCI (4, 5). According to McKee et al. (23), out of 65 CTE subjects with a history of repetitive mTBIs (rmTBIs), 30 (46.2%) exhibited pathological comorbidities, including AD, motor neuron disease (MND), PD, Lewy body disease (LBD), FTLD, Pick's disease, and progressive supranuclear palsy (PSP). There are many questions we cannot help but ask: why does the same reason (TBI) lead to different outcomes (different types of diseases)? Does it suggest a shared pathogenic mechanism in the onset of these diseases post-TBI? Moreover, TBI appears to cause the most measurable strain and mechanical deformation at the depth of the cortical sulcus and around small vessels (67), where the pathognomonic lesion of CTE (hyperphosphorylated tau) also appears (24, 68). The alterations in the early stages of TBI seem to be induced primarily by initial axon injury, which could arouse and prompt a series of secondary damages, such as neuroinflammation and proteinopathies, leading to an increased risk of neurodegeneration (53, 70). The deposit of TDP-43 (TAR DNA-binding protein 43) and tau in the neocortex, medial temporal lobes, and deeper brain structures might be linked to cognitive, memory, and behavior changes, as well as parkinsonism. And cortical regions with a greater TDP-43 pathological burden might be associated with cognitive impairment in CTE patients (22). It is reasonable to speculate that TBI causes axonal injury across multiple regions of the brain, where the initial axonal injury would contribute to the accumulation of toxic proteins and other secondary injurious responses, further leading to the onset and

progression of neurodegenerative diseases, such as dementia. And the different manifestations in TBI patients might reflect impairments in diverse spatial locations of the CNS resulting from similar pathogenic mechanisms (71). However, further research is required to deepen our understanding of post-TBI dementia.

Graham et al. (72) conducted a comparative study on the patterns of neurodegeneration in moderate to severe TBI patients with those suffering from AD. The study spanned a median duration of 2.1 years after the injury. With respect to the brain regions with progressive atrophy, their findings indicated a visible overlap between TBI and AD patients in part of the white matter (WM), predominantly subcortical regions rather than deep WM structures. In contrast, the gray matter (GM) exhibited no significant overlap. And "TBI-specific" areas with significant atrophy included "the corona radiata, the corpus callosum, the corticospinal tracts, and so on," while "AD-specific" regions included "temporal GM, parietal and occipital cortices," as well as parts of the WM. The findings of this study suggest that distinct patterns of atrophy occur in AD and following TBI, and TBI could significantly affect the subcortical and deep WM structures. However, the situation is discordant in mTBI. Zhou et al. (73) explored the brain volume change of mTBI patients with an average follow-up time of 1 year and 1 month. They found significantly reduced brain volumes in the anterior cingulate WM, the left cingulate gyrus isthmus WM, and the right precuneus GM in mTBI patients compared with healthy control subjects. And the volume loss in the rostral anterior cingulate WM might be relevant to poor neurocognitive performance. Shida et al. (74) analyzed the effect of mTBI on brain aging, especially the loss of GM volume, based on MRI images around 6 months post-TBI. They observed that the average biological age of brain areas in mTBI patients was 9.2 years older than that of healthy controls. The regional GM most significantly affected by mTBI involved "the short gyri, long gyrus, and central sulcus of the insula." Rostowsky et al. (75) compared the neurodegeneration 6 months post mTBI with that of AD and observed a significant overlap of abnormal brain regions, in both cases, not only in parts of WM but also in parts of GM, which indicated that the effects of mTBI on the brain might be different from that observed in cases of moderate and severe TBI, further supporting the idea that TBIs of different severity have distinct pathogenic mechanisms. The pattern of neurodegeneration following TBI should be further investigated to fully compare TBI with AD and other neurodegenerative disorders. Additionally, examining TBI patients with favorable outcomes might conduce to identifying protective factors and understanding the progression of post-TBI dementia and other neurodegenerative diseases (69).

Conclusion

In conclusion, post-TBI dementia has raised great interest among neuroscientists, pathologists, and neurologists, among others, worldwide, and abundant studies, focusing on the field, are being conducted each year. The United States is the dominant country in this area in nearly all respects, including the number of publications, prestigious scientists, and notable institutes. The United Kingdom and Canada also have great influence and involvement in this field. Despite having the second-largest number of articles, the prestige of China underperforms. China should focus on participating in more international research cooperation. The hot spots in this field include "The correlation between TBI and dementia-related alteration" and "CTE." Moreover, researchers are also focusing their attention on clinical manifestation, therapy, pathology, and pathogenic mechanisms. In summary, the study provides valuable insights into the current status and progression of the discipline, which is expected to inform and improve future research in this area.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

HR and L-JH determined the theme of the study. X-ZS, C-QW, and WC designed the study, scrutinized the data, wrote the manuscript, and made the figures and tables. X-ZS and C-QW collected data. The bibliometric analysis-related software and the online platform were operated by X-ZS and WC. Data analysis and interpretation were done by X-ZS, C-QW, WC, HR, and L-JH. WC, C-QW, HR, and L-JH revised the article. Bibliometrics-related guidance was from HR. Medicine-related guidance was from L-JH and HR. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1165059/full#supplementary-material

References

1. Tagge CA, Fisher AM, Minaeva OV, Gaudreau-Balderrama A, Moncaster JA, Zhang XL, et al. Concussion, microvascular injury, and early tauopathy in young athletes after impact head injury and an impact concussion mouse model. *Brain*. (2018) 141:422–58. doi: 10.1093/brain/awx350

2. Stopa BM, Tahir Z, Mezzalira E, Boaro A, Khawaja A, Grashow R, et al. The impact of age and severity on dementia after traumatic brain injury: A comparison study. *Neurosurgery*. (2021) 89:810–8. doi: 10.1093/neuros/nyab297

3. Osler M, Rozing MP, Eliasen MH, Christensen K, Mortensen EL. Traumatic brain injury and risk of dementia at different levels of cognitive ability and education. *Eur J Neurol*. (2020) 27:399–405. doi: 10.1111/ene.14095

4. Leung KK, Carr FM, Russell MJ, Bremault-Phillips S, Triscott JAC. Traumatic brain injuries among veterans and the risk of incident dementia: A systematic review & meta-analysis. *Age Ageing*. (2022) 51:afab194. doi: 10.1093/ageing/afab194

5. Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, Boeve BF, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J Neurosurg*. (2016) 124:511–26. doi: 10.3171/2015.2.JNS14503

6. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet commission. *Lancet*. (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6

7. Barr WB. POINT/COUNTER-POINT-links between traumatic brain injury and dementia remain poorly defined. *Arch Clin Neuropsychol*. (2020) 35:128–32. doi: 10.1093/arclin/acz075

8. Grasset L, Glymour MM, Yaffe K, Swift SL, Gianattasio KZ, Power MC, et al. Association of traumatic brain injury with dementia and memory decline in older adults in the United States. *Alzheimers Dement*. (2020) 16:853–61. doi: 10.1002/alz.12080

9. Nguyen TP, Schaffert J, LoBue C, Womack KB, Hart J, Cullum CM. Traumatic brain injury and age of onset of dementia with Lewy bodies. *J Alzheimers Dis*. (2018) 66:717–23. doi: 10.3233/JAD-180586

10. Plassman BL, Chanti-Ketterl M, Pieper CF, Yaffe K. Traumatic brain injury and dementia risk in male veteran older twins-controlling for genetic and early life non-genetic factors. *Alzheimers Dement*. (2022) 18:2234–42. doi: 10.1002/alz.12571

11. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. (2018) 130:1080–97. doi: 10.3171/2017.10.JNS17352

12. Choudhri AF, Siddiqui A, Khan NR, Cohen HL. Understanding bibliometric parameters and analysis. *Radiographics*. (2015) 35:736–46. doi: 10.1148/rg.2015140036

13. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics*. (2010) 84:523–38. doi: 10.1007/s11192-009-0146-3

14. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci U S A*. (2004) 101:5303–10. doi: 10.1073/pnas.0307513100

15. CiteSpace II CC. Detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inform Sci Technol*. (2006) 57:359–77. doi: 10.1002/asi.20317

16. Li K, Rollins J, Yan E. Web of science use in published research and review papers 1997-2017: a selective, dynamic, cross-domain, content-based analysis. *Scientometrics*. (2018) 115:1–20. doi: 10.1007/s11192-017-2622-5

17. Tu JX, Lin XT, Ye HQ, Yang SL, Deng LF, Zhu RL, et al. Global research trends of artificial intelligence applied in esophageal carcinoma: A bibliometric analysis (2000-2022) via CiteSpace and VOSviewer. *Front Oncol*. (2022) 12:972357. doi: 10.3389/fonc.2022

18. Zhang F, Wang R, Liu B, Zhang L. A bibliometric analysis of autophagy in atherosclerosis from 2012 to 2021. *Front Pharmacol*. (2022) 13:977870. doi: 10.3389/fphar.2022

19. Merton RK. The Matthew effect in science. The reward and communication systems of science are considered. *Science*. (1968) 159:56–63. doi: 10.1126/science.159.3810.56

20. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature*. (2012) 485:512–6. doi: 10.1038/nature11087

21. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol*. (2016) 15:455–532. doi: 10.1016/S1474-4422(16)00062-4

22. McKee AC, Gavett BE, Stern RA, Nowinski CJ, Cantu RC, Kowall NW, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. (2010) 69:918–29. doi: 10.1097/NEN.0b013e3181ee7d85

23. McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. (2013) 136:43–64. doi: 10.1093/brain/aws307

24. McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*. (2016) 131:75–86. doi: 10.1007/s00401-015-1515-z

25. Mez J, Daneshvar DH, Kiernan PT, Abdolmohammadi B, Alvarez VE, Huber BR, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*. (2017) 318:360–70. doi: 10.1001/jama.2017.8334

26. Stein TD, Montenigro PH, Alvarez VE, Xia W, Crary JF, Tripodis Y, et al. Beta-amyloid deposition in chronic traumatic encephalopathy. *Acta Neuropathol*. (2015) 130:21–34. doi: 10.1007/s00401-015-1435-y

27. Stern RA, Daneshvar DH, Baugh CM, Seichepine DR, Montenigro PH, Riley DO, et al. Clinical presentation of chronic traumatic encephalopathy. *Neurology*. (2013) 81:1122–9. doi: 10.1212/WNL.0b013e3182a55f7f

28. Bieniek KF, Ross OA, Cormier KA, Walton RL, Soto-Ortolaza A, Johnston AE, et al. Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathol*. (2015) 130:877–89. doi: 10.1007/s00401-015-1502-4

29. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz JB, Keene CD, et al. Association of Traumatic Brain Injury with Late-Life Neurodegenerative Conditions and Neuropathologic Findings. *JAMA Neurol*. (2016) 73:1062–9. doi: 10.1001/jamaneurol.2016.1948

30. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol*. (2014) 71:1490–7. doi: 10.1001/jamaneurol.2014.2668

31. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat Rev Neurol*. (2013) 9:211–21. doi: 10.1038/nrneurol.2013.29

32. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. *Neurology*. (2014) 83:312–9. doi: 10.1212/WNL.0000000000000616

33. Nordstrom P, Michaelsson K, Gustafson Y, Nordstrom A. Traumatic brain injury and young onset dementia: a nationwide cohort study. *Ann Neurol*. (2014) 75:374–81. doi: 10.1002/ana.24101

34. Goldstein LE, Fisher AM, Tagge CA, Zhang XL, Velisek L, Sullivan JA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci Transl Med*. (2012) 4:134ra60. doi: 10.1126/scitranslmed.3003716

35. McKee AC, Daneshvar DH, Alvarez VE, Stein TD. The neuropathology of sport. *Acta Neuropathol*. (2014) 127:29–51. doi: 10.1007/s00401-013-1230-6

36. McKee AC, Stein TD, Kiernan PT, Alvarez VE. The neuropathology of chronic traumatic encephalopathy. *Brain Pathol*. (2015) 25:350–64. doi: 10.1111/bpa.12248

37. Montenigro PH, Baugh CM, Daneshvar DH, Mez J, Budson AE, Au R, et al. Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimers Res Ther*. (2014) 6:68. doi: 10.1186/s13195-014-0068-z

38. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of Mild Traumatic Brain Injury with and without Loss of consciousness with dementia in US military veterans. *JAMA Neurol*. (2018) 75:1055–61. doi: 10.1001/jamaneurol.2018.0815

39. Fann JR, Ribe AR, Pedersen HS, Fenger-Gron M, Christensen J, Benros ME, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. *Lancet Psychiatry*. (2018) 5:424–31. doi: 10.1016/S2215-0366(18)30065-8

40. Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. *PLoS Med*. (2018) 15:e1002496. doi: 10.1371/journal.pmed.1002496

41. Ramos-Cejudo J, Wisniewski T, Marmar C, Zetterberg H, Blennow K, de Leon MJ, et al. Traumatic brain injury and Alzheimer's disease: the cerebrovascular link. *EBioMedicine*. (2018) 28:21–30. doi: 10.1016/j.ebiom.2018.01.021

42. Atherton K, Han X, Chung J, Cherry JD, Baucom Z, Saltiel N, et al. Association of APOE genotypes and chronic traumatic encephalopathy. *JAMA Neurol*. (2022) 79:787–96. doi: 10.1001/jamaneurol.2022.1634

43. Redelmeier DA, Manzoor F, Thiruchelvam D. Association between statin use and risk of dementia after a concussion. *JAMA Neurol*. (2019) 76:887–96. doi: 10.1001/jamaneurol.2019.1148

44. Farzanegan GR, Derakhshan N, Khalili H, Ghaffarpasand F, Paydar S. Effects of atorvastatin on brain contusion volume and functional outcome of patients with moderate and severe traumatic brain injury; a randomized double-blind placebo-controlled clinical trial. *J Clin Neurosci*. (2017) 44:143–7. doi: 10.1016/j.jocn.2017.06.010

45. Li M, Reisman J, Morris-Eppolito B, Qian SX, Kazis LE, Wolozin B, et al. Beneficial association of angiotensin-converting enzyme inhibitors and statins on the occurrence of possible Alzheimer's disease after traumatic brain injury. *Alzheimers Res Ther*. (2020) 12:33. doi: 10.1186/s13195-020-00589-3

46. DeKosky ST, Asken BM. Injury cascades in TBI-related neurodegeneration. *Brain Inj*. (2017) 31:1177–82. doi: 10.1080/02699052.2017.1312528

47. Edwards G 3rd, Moreno-Gonzalez I, Soto C. Amyloid-beta and tau pathology following repetitive mild traumatic brain injury. *Biochem Biophys Res Commun*. (2017) 483:1137–42. doi: 10.1016/j.bbrc.2016.07.123

48. Ma X, Aravind A, Pfister BJ, Chandra N, Haorah J. Animal models of traumatic brain injury and assessment of injury severity. *Mol Neurobiol*. (2019) 56:5332–45. doi: 10.1007/s12035-018-1454-5

49. Martland HS. Punch drunk. *J Am Med Assoc*. (1928) 91:1103–7. doi: 10.1001/jama.1928.02700150029009

50. Smith DH, Johnson VE, Trojanowski JQ, Stewart W. Chronic traumatic encephalopathy - confusion and controversies. *Nat Rev Neurol*. (2019) 15:179–83. doi: 10.1038/s41582-018-0114-8

51. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery*. (2005) 57:128–134; discussion 128–34. doi: 10.1227/01.neu.0000163407.92769.ed

52. Schneider ALC, Selvin E, Liang M, Latour L, Turtzo LC, Koton S, et al. Association of Head Injury with brain amyloid deposition: the ARIC-PET study. *J Neurotrauma*. (2019) 36:2549–57. doi: 10.1089/neu.2018.6213

53. Collins-Praino LE, Corrigan F. Does neuroinflammation drive the relationship between tau hyperphosphorylation and dementia development following traumatic brain injury? *Brain Behav Immun*. (2017) 60:369–82. doi: 10.1016/j.bbi.2016.09.027

54. Gavett BE, Stern RA, Cantu RC, Nowinski CJ, McKee AC. Mild traumatic brain injury: a risk factor for neurodegeneration. *Alzheimers Res Ther*. (2010) 2:18. doi: 10.1186/alzrt42

55. Mariani M, Alosco ML, Mez J, Stern RA. Clinical presentation of chronic traumatic encephalopathy. *Semin Neurol*. (2020) 40:370–83. doi: 10.1055/s-0040-1713624

56. McFadyen CA, Zeiler FA, Newcombe V, Synnot A, Steyerberg E, Gruen RL, et al. Apolipoprotein E4 polymorphism and outcomes from traumatic brain injury: A living systematic review and Meta-analysis. *J Neurotrauma*. (2021) 38:1124–36. doi: 10.1089/neu.2018.6052

57. Nalivaeva NN, Zhuravin IA, Turner AJ. Neprilysin expression and functions in development, ageing and disease. *Mech Ageing Dev*. (2020) 192:111363. doi: 10.1016/j.mad.2020

58. Maigler KC, Buhr TJ, Park CS, Miller SA, Kozlowski DA, Marr RA. Assessment of the effects of altered amyloid-Beta clearance on behavior following repeat closed-head brain injury in amyloid-Beta precursor protein humanized mice. *J Neurotrauma*. (2021) 38:665–76. doi: 10.1089/neu.2020.6989

59. Eric Nyam TT, Ho CH, Chio CC, Lim SW, Wang JJ, Chang CH, et al. Traumatic brain injury increases the risk of major adverse cardiovascular and cerebrovascular events: A 13-year, population-based study. *World Neurosurg*. (2019) 122:e740–753. doi: 10.1016/j.wneu.2018.10.130

60. Kumar RG, Juengst SB, Wang Z, Dams-O'Connor K, Dikmen SS, O'Neil-Pirozzi TM, et al. Epidemiology of comorbid conditions among adults 50 years and older with traumatic brain injury. *J Head Trauma Rehabil*. (2018) 33:15–24. doi: 10.1097/HTR.0000000000000273

61. Hammond FM, Corrigan JD, Ketchum JM, Malec JF, Dams-O'Connor K, Hart T, et al. Prevalence of medical and psychiatric comorbidities following traumatic brain injury. *J Head Trauma Rehabil*. (2019) 34:E1–E10. doi: 10.1097/HTR.0000000000000465

62. Qi B, Jin S, Qian H, Zou Y. Bibliometric analysis of chronic traumatic encephalopathy research from 1999 to 2019. *Int J Environ Res Public Health*. (2020) 17:5411. doi: 10.3390/ijerph17155411

63. Omalu BI, DeKosky ST, Hamilton RL, Minster RL, Kamboh MI, Shakir AM, et al. Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery*. (2006) 59:1086–1092; discussion 1092–1093. doi: 10.1227/01.NEU.0000245601.69451.27

64. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology*. (2000) 55:1158–66. doi: 10.1212/wnl.55.8.1158

65. Snyder HM, Carare RO, DeKosky ST, de Leon MJ, Dykxhoorn D, Gan L, et al. Military-related risk factors for dementia. *Alzheimers Dement*. (2018) 14:1651–62. doi: 10.1016/j.jalz.2018.08.011

66. Godbolt AK, Cancelliere C, Hincapie CA, Marras C, Boyle E, Kristman VL, et al. Systematic review of the risk of dementia and chronic cognitive impairment after mild traumatic brain injury: results of the international collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil*. (2014) 95:S245–56. doi: 10.1016/j.apmr.2013.06.036

67. McKee AC, Stein TD, Huber BR, Crary JF, Bieniek K, Dickson D, et al. Chronic traumatic encephalopathy (CTE): criteria for neuropathological diagnosis and relationship to repetitive head impacts. *Acta Neuropathol*. (2023) 145:371–94. doi: 10.1007/s00401-023-02540-w

68. Bieniek KF, Cairns NJ, Crary JF, Dickson DW, Folkerth RD, Keene CD, et al. The second NINDS/NIBIB consensus meeting to define Neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. (2021) 80:210–9. doi: 10.1093/jnen/nlab001

69. Dams-O'Connor K, Awwad HO, Hoffman SW, Pugh MJ, Johnson V, Keene CD, et al. Zetterberg H. Alzheimer's disease-related dementias summit 2022: national research priorities for the investigation of post-traumatic brain injury Alzheimer's disease and related dementias. *J Neurotrauma*. (2023). doi: 10.1089/neu.2022.0514

70. Graham NSN, Jolly A, Zimmerman K, Bourke NJ, Scott G, Cole JH, et al. Diffuse axonal injury predicts neurodegeneration after moderate-severe traumatic brain injury. *Brain*. (2020) 143:3685–98. doi: 10.1093/brain/awaa316

71. Geser F, Martinez-Lage M, Robinson J, Uryu K, Neumann M, Brandmeir NJ, et al. Clinical and pathological continuum of multisystem TDP-43 proteinopathies. *Arch Neurol*. (2009) 66:180–9. doi: 10.1001/archneurol.2008.558

72. Graham NSN, Cole JH, Bourke NJ, Schott JM, Sharp DJ. Distinct patterns of neurodegeneration after TBI and in Alzheimer's disease. *Alzheimers Dement*. (2023). doi: 10.1002/alz.12934

73. Zhou Y, Kierans A, Kenul D, Ge Y, Rath J, Reaume J, et al. Mild traumatic brain injury: longitudinal regional brain volume changes. *Radiology*. (2013) 267:880–90. doi: 10.1148/radiol.13122542

74. Shida AF, Massett RJ, Imms P, Vegesna RV, Amgalan A, Irimia A, et al. Significant acceleration of regional brain aging and atrophy after mild traumatic brain injury. *J Gerontol A Biol Sci Med Sci*. (2023). doi: 10.1093/gerona/glad079

75. Rostowsky KA, Irimia AAlzheimer's Disease Neuroimaging I. Acute cognitive impairment after traumatic brain injury predicts the occurrence of brain atrophy patterns similar to those observed in Alzheimer's disease. *Geroscience*. (2021) 43:2015–39. doi: 10.1007/s11357-021-00355-9

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Post-traumatic olfactory dysfunction: a scoping review of assessment and rehabilitation approaches

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Post-traumatic Olfactory Dysfunction (PTOD) consists of a complete or partial loss of olfactory function that may occur after a traumatic brain injury (TBI). PTOD may be linked to some neuropsychiatric features, such as social, cognitive and executive dysfunction, as well as behavioral symptoms, especially when TBI involves the orbito-frontal cortex. The diagnosis of PTOD is based on medical history and clinical data and it is supported by psychometric tests (i.e., subjective tools) as well as electrophysiological and neuroimaging measures (i.e., objective methods). The assessment methods allow monitoring the changes in olfactory function over time and help to establish the right therapeutic and rehabilitative approach. In this context, the use of the olfactory training (OT), which is a non-pharmacological and non-invasive treatment option, could promote olfactory function through top-down (central) and bottom-up (peripheral) processes. To better manage patients with TBI, PTOD should be detected early and properly treated using the various therapeutic rehabilitative possibilities, both conventional and advanced, also taking into consideration the emerging neuromodulation approach.

KEYWORDS

post-traumatic olfactory dysfunction, neurorehabilitation, traumatic brain injury, olfactory training, olfactory assessment

1. Introduction

Traumatic brain injury (TBI) is a leading cause of significant public health problems, since it often causes high disability and mortality rates. Indeed, TBI is often associated with physical and sensory disturbances, including not only the well-known auditory and visual disorders, but also olfactory problems, which are instead poorly investigated (1). Post-traumatic Olfactory Dysfunction (PTOD) is commonly described as the complete or partial loss of olfactory function due to the block of nasal nerve passages, olfactory nerve injury or concussions or hemorrhages in the olfactory centers of the brain (2). Prognosis of olfactory dysfunction depends on the etiologies because conductive smell loss shows a good prognosis after intervention compared to sensory-neural type. Bratt et al. (3) found that 8% of patients with moderate or severe TBI had anosmia, and 14% had olfactory dysfunctions lasting years after the trauma. The likelihood of PTOD has been linked to both the severity of injury and length of post-traumatic amnesia (4). PTOD can occur in 0–16% of patients with mild TBI, 15–19% of those with moderate TBI, and 25–30% of those with severe TBI (5), especially in terms of the perception of smell changes, It

has been suggested that the site of injury could be strictly related to olfactory dysfunction. In fact, results from morphological magnetic resonance image (MRI) studies in PTOD patients pointed out that brain lesions were localized in the orbito-frontal, olfactory frontal cortex, and temporal lobes (6). Generally, PTOD is linked to some neuropsychiatric disorders including anxiety, depression, and impulsivity, especially when TBI occurs in the orbito-frontal (ventral prefrontal) areas (7, 8). In this way, PTOD leads to lower quality of life (QoL) compared to TBI patients without olfactory dysfunction, also because of the fear of exposure to hazardous substances (9, 10).

Indeed neuroanatomical and kinetic factors make the peripheral and central olfactory structures more susceptible to damage when TBI occurs, as reflected by the high prevalence (11) of PTOD and the related psychological and cognitive – behavioral symptoms. Traumatic facial and brain injury due to blast and incidents are common causes of smell alterations, including total loss of function (anosmia), decreased sensitivity (hyposmia), alterations in odor quality (dysosmia/parosmia) and hallucination (phantosmia) (12). In some cases, brain damage limited to the primary olfactory areas leads to anosmia, while damage to the orbitofrontal cortex provokes olfactory discrimination and recognition deficits due to the multisensory integration role of this brain area (13). In a more specific way, anosmia can be considered as manifestation of frontal lobe damage, and it is correlated with alterations in verbal fluency abilities and executive functions (14, 15). Other authors (16) found that anosmia is strongly associated with depression symptoms in TBI patients, likely for the anatomical relationship between the two functions. The orbital frontal cortex plays a key role in both mood regulation and recognition and differentiation of odors (17). Moreover, hyposmia could be accompanied by socially disinhibited behavioral alteration, which is likely linked to orbital frontal cortex damage, as for the cognitive deficits (18). Moreover, Neumann et al. (19) reported that 56% of moderate to severe TBI presented dysosmia/parosmia in addition to difficulty in interpreting facial expressions and emotions.

These authors identified that cognitive-emotional networks, which are important for recognition and empathy, were also involved in central olfactory functions suggesting that this may be related to more complex social functions. It has been hypothesized that dysosmia/parosmia and depressive and anxiety symptoms are linked to persisting alterations of frontotemporal structures, such as the hippocampus and the orbitofrontal cortex (20, 21), as demonstrated by neuroimaging studies (22, 23). Phantosmia has been described as an olfactory disturbance in which individuals perceive an odor in the absence of a stimulus that may disappear, improve or worsen over time (24–26).

Various medical treatments have been tried to improve PTOD, including topical and systemic steroids, but well-controlled studies still lack (27).

Other drugs such as Gingko biloba and vitamin B have not proven to be effective to treat olfactory dysfunction (28).

Although there are limited therapeutic options for patients with PTOP, about 16.8 to 27% of patients may experience some degree of spontaneous recovery, which is mainly due to the high degree of neuroplasticity of the olfactory system (29, 30).

Natural smell recovery mostly occurs within 1 year after the traumatic event. However, the chances of improvement are reduced after 2 years from PTOD. Olfactory training might be a promising modality for the treatment of PTOD. In this context, different studies (31, 32) have indicated the effectiveness of olfactory training (OT), i.e., daily exposure to certain odors, thanks to the possibility of boosting neural plasticity of the olfactory system.

The diagnosis of smell disorders is suspected by medical history and supported by clinical data as well as by the results of psychophysiological, electrophysiological and neuroimaging measures. Among the validated psychophysical tests, the Sniffin' Sticks Test (SST) is the most commonly and widely used tool. A more objective and quantitative measurement of sensory smell loss following TBI can be recorded though the Olfactory Event-Related Potentials (OERPs), which allows one to observe electrophysiologically the function of the olfactory system and its changes (33, 34).

In a forensic traumatic event, the clinical picture and severity of the person need to be determined with the use of objective criteria, although there are still limitations in objectively evaluating olfactory dysfunctions and state the relationship between the event and its cause. Performing both subjective and electrophysiological tests together to detect olfactory dysfunctions that occur after a forensic incident enable provide more reliable results in diagnosis and treatment (35). The OERPs method may provide objective data in the evaluation of post traumatic anosmia from the medicolegal perspective, to identify specific factors and the degree of smell loss (36).

The aim of this review is to investigate the main features of PTOD, focusing on the assessment through subjective and objective tools, emphasizing at the same time, the role of the main rehabilitative approaches to treat smell impairments following TBI.

2. Methods

2.1. Search strategy

The studies included in this review were identified by searching on PubMed, Scopus, Web of Science and Cochrane library, using the following keywords: "post-traumatic olfactory dysfunction" OR "olfactory dysfunction in traumatic brain injury" AND "post-traumatic olfactory dysfunctions and cognitive manifestations" AND "post-traumatic olfactory dysfunction diagnosis" OR "post-traumatic olfactory dysfunction assessment" AND "olfactory rehabilitative training in traumatic brain injury" OR "post-traumatic olfactory dysfunction rehabilitation."

2.2. PICO evaluation

We defined the search terms using the PICO (population, intervention, comparison, outcome) model. We considered patients affected by PTOD as population; intervention included both assessment tools and rehabilitation approaches (conventional or not) for PTOD; comparison consisted in other kind of tool/medication used to assess/treat PTOD; the outcome measures considered were smell recovery, quality of life and any kind of improvement in olfactory function, including neuroplasticity.

2.3. Inclusion and exclusion criteria

The inclusion criteria were (i) patients affected by moderate to severe TBI with OD; (ii) randomized clinical trials (RCT), pilot studies

and systematic reviews, case control and retrospective studies published between January 2012 and September 2022; (iii) English language; and (iv) papers published in a peer-reviewed journal. Exclusion criteria were (i) case reports and narrative reviews; (ii) studies describing other kinds of post-traumatic dysfunctions; (iii) studies involving children and adolescents affected by PTOD; (iv) other etiology of OD (i.e., vascular accidents, ischemic and/or hemorrhagic, neurodegenerative).

2.4. Literature selection

Besides the papers themselves, we have analyzed the references of the selected articles, (but including only English papers), in order to obtain a complete search. The studies fulfilling our selected criteria and published between 2012 and 2022 were evaluated for possible inclusion ($n = 198$). Then, we have considered only English papers and removed duplicates ($n = 100$) (see Figure 1). Two reviewers (RDL and MB), have evaluated articles according to title, abstracts and text, and finally we considered 35 articles that addressed the main PTOD assessment tools and rehabilitative approaches.

2.5. Data extraction

In details, two reviewers (R.D.L. and M.B.) extracted data under the following categories: (i) measure characteristics (i.e., purpose, target population, time of test execution), (ii) psychometric properties of each assessment tool according to the information reported by the available studies and (iii) type of rehabilitative intervention used by the selected studies.

3. Subjective and objective assessment methods in olfaction

Recently, researchers made significant progress in the development of widely available, reliable, and reproducible methods to evaluate olfactory function. The administration of these tools is essential to establish the degree of chemosensory loss and confirm the patient's complaint of olfactory alteration (37). Indeed, it permits monitoring the OD changes over time in post-TBI patients and helps to establish the right therapeutic and rehabilitative choice, considering also its impact on the patient's treatment and counseling (38). Two main types of olfactory testing are commonly used: subjective tools, which include psychometric scales/tests (Table 1), and objective methods such as electrophysiological testing (Table 2) (62).

Among the subjective examinations of olfaction, some screening tools are useful to differentiate easily and rapidly patients with normosmia, hyposmia or anosmia. In clinical practice, the most used screening tool for TBI-related olfactory dysfunctions is the Sniffin' Sticks test, developed by Hummel in 1997, which contains some marker pens to be smelled, and it takes approximately 4 min to be administered. Concerning the recognition part, this validated test can be easily administered also in patients with language alterations (i.e., in the presence of aphasia) thanks to a wordlist of odors or non-verbal information like photographs/drawings representing smells. However, it requires good cooperation by the patient, who must pay attention during the test (39, 63).

When clinicians need to further investigate odor identification, discrimination and thresholds, a more extensive and detailed testing can be used (64) Indeed, the University of Pennsylvania Smell Identification Test (UPSIT), developed in the early 1980's, focuses on the comparative ability of individuals to identify odors at the suprathreshold level (40–42).

It was administered also in Parkinson disease's (PD) population and in patients with COVID-19 to reveal changes in the olfactory function (43–46).

Despite its high reliability ($r = 0.94$), the UPSIT has shown poor sensitivity for malingering detection in people familiar with the test mechanism.

The Connecticut Test, in which the odor stimulus is contained in suitable glass flasks (47) is quite similar to the Brief-Smell Identification Test (see Table 1), which is administered in older people and can be used for the evaluation and diagnosis of patients with olfactory impairments, considering the advantage of its low cost. An important issue about CCCRC is that low scores can be indicative of TBI, while abnormal detection thresholds may reflect altered olfactory cell function (49). Langdon et al. (48) evaluated severe smell loss in TBI patients using the Barcelona Smell Test (BAST-24), validated for the Catalan and Spanish population. It consists of 24 odors scoring smell detection, identification, and forced choice, and according to Cartesin et al., the tool is a good and reliable method to test the olfactory function in clinical practice (47).

Another specific test that can be administered to determine olfactory function in a rapid and non-invasive manner is the n-Butanol Threshold Test (n-BTt) (48, 65). Denzer et al. (50) used sniffing sticks with n-Butanol to investigate smell function, when generally this test is administered through gas chromatographic methods. The authors revealed that a pen set with n-butanol is an appropriate tool for testing olfactory sensitivity.

During the administration of self-assessment tools, there are three factors to consider: (i) odor threshold, (ii) odor discrimination, and (iii) odor identification (51, 52).In a recent study, Limphaibool et al. (2020) described a subjective olfactory examination, named the blast (Elsberg-Levy) olfactometry, which is a popular method of olfactory threshold measurement (34), in addition to the administration of main Fragrances Used in Olfactometer Test. The specific odors are mint (100% natural menthe piperita oil) and anise (100% natural *Illicium Verum* Seed Oil) at the temperature of 21 ± 1 degrees Celsius. Notably, anise oil is administered to stimulate the olfactory nerve endings whereas mint oil promotes the activation of both the olfactory and trigeminal nerve endings in the nasal mucosal tissue (66). Despite its usefulness in detecting olfactory thresholds, the blast (Elsberg-Levy) olfactometry may provide false results in smell performance due to the presence of odorant-free air, which could stimulate trigeminal nerve sensors (67).

Interestingly, Sattin (68) investigated olfactory function in patients affected by disorders of consciousness (DOC) due to TBI, using an olfactory discrimination protocol (ODP). This ODP was composed of four odors, selected and dosed according to both the literature on clinical sniff tests and to functional magnetic resonance, assessing the olfactory neural process and pathways (69–71). Given that the olfactory receptors are implicated in processing memory (which

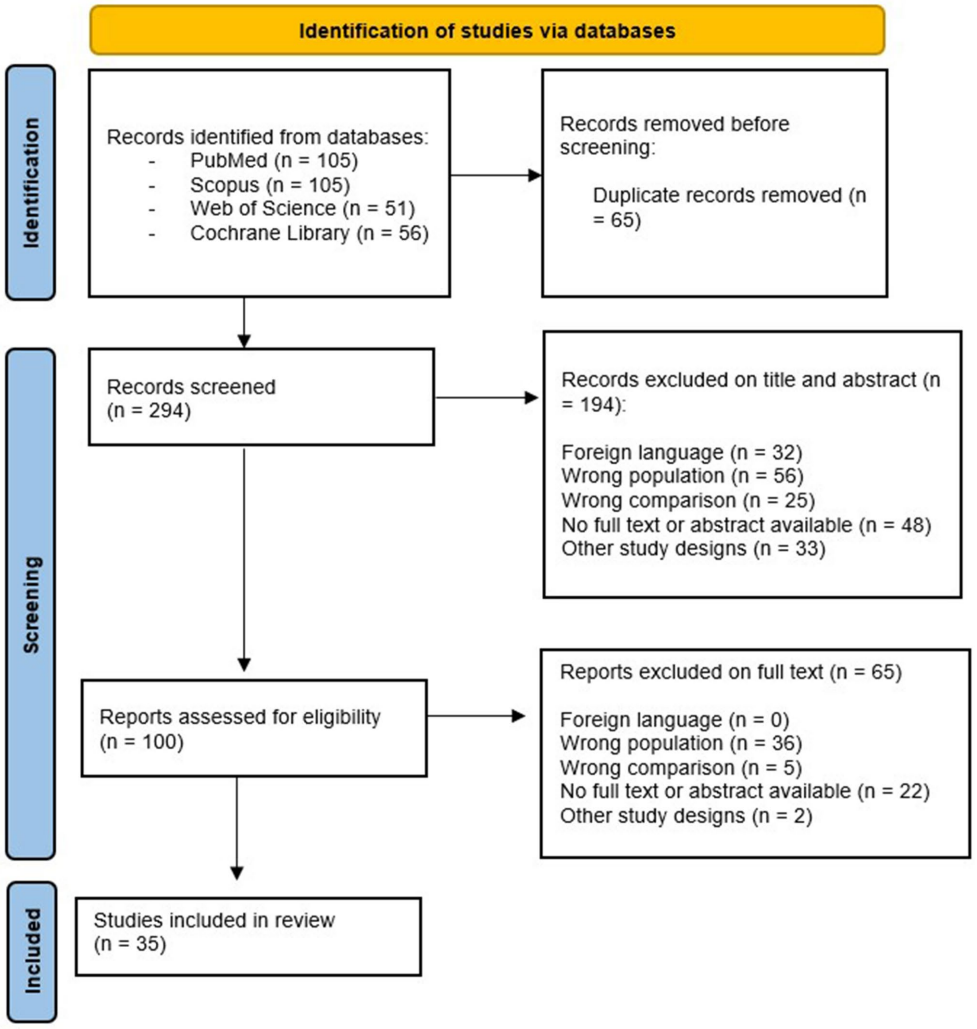

FIGURE 1
PRISMA flow chart for attrition of the papers, which were used in the final review.

involves amygdala, hippocampus, etc.), olfaction could be a simple and direct way to stimulate memory and emotions in DOC.

Langdon et al. (48) administered the SNOT-22 as an additional/complementary outcome measure to investigate QoL in PTOD patients. In fact, the tool seems particularly useful in detecting changes in QoL according to smell symptoms (53, 54). In this vein, Neumann et al. (19) investigated the PTOD in moderate and severe TBI by assessing also emotional sequelae, through the administration of a complete battery, which included: (i) Olfaction (Brief Smell Identification Test-BSIT) (41); (ii) facial affect recognition [Diagnostic Assessment of Nonverbal Affect 2-Adult Faces (DANVA2-AF)] (55); (iii) vocal affect recognition [Diagnostic Assessment of Nonverbal Affect 2-Adult Paralanguage (DANVA2-AP)] (56); (iv) emotional inference [Emotional Inference from Stories Test (EIST)] (57) and (v) empathy [Interpersonal Reactivity Index (IRI)] (58). The authors showed that the detection of olfactory dysfunction may be related to affect and empathy deficits (59, 60). This is why an early assessment of these emotional impairments could be useful to set the most appropriate treatment for PTOD patients.

An objective examination (Table 2) may be indeed useful to more accurately identify olfactory defects.

Olfactory Event-related potentials (OERPs) are a reliable electrophysiological instrument to detect changes in olfactory function in an objective view. The recording device for cortical evoked potentials and odor stimulator, according to the above-mentioned Elsberg Levy method, can be also considered an objective olfactory evaluation (61). Compared to other methods such as MRI or fMRI, OERP measurements also have a higher temporal resolution, and can be conducted at lower cost with a lower degree of invasiveness (72).

Some authors have used OERPs to evaluate olfactory function in different patient populations such as multiple sclerosis (73) Alzheimer's disease and other dementias (74–76), Parkinson's disease (77), older people (78, 79), and as a marker for depression (80). However, other authors believe that these techniques are complex, time-consuming and not routinely performed in clinical practice (81). Notably, Shiga et al. used SPECT-MRI with Nasal Thallium-201 administration to identify lesions of the olfactory nerve connectivity in patients with impaired olfaction. In fact, these authors noticed that

TABLE 1 The main subjective measures and complementary/additional tools to assess olfactory dysfunctions following TBI.

Subjective olfactory measures	Description
Screening tools	
Sniffin' Sticks (SS)	Sniffin' Sticks (SS) is a screening nasal test to evaluate smell function. It consists of a tool similar to a pen, which dispenses odors. It includes three tests: (i) for odor threshold (n-butanol, through one staircase), (ii) odor discrimination (through 16 pairs of smells, triple forced choice) and (iii) odor identification (16 common odorants, multiple forced choice from four verbal items per test odorant) (34). In particular, the SS presents a specific test–retest reliability for each subtest: $r = 0.80$ (odor discrimination), $r = 0.88$ (odor identification), and $r = 0.92$ (odor threshold). In addition, the SS's sensitivity and specificity is about 84% of the total score (39, 40).
Brief Smell Identification Test (BSIT)	The Brief Smell Identification Test (BSIT) is an abbreviated version of the Smell Identification Test (SIT) used to measure olfactory function, especially in elderly population as possible clinical marker in Alzheimer disease (41). The BSIT is often used to screen olfactory function in elderly population. The execution takes about 5 min, including 12 different odors within scented strips and released when scratched with the tip of pencil. Each participant is submitted to a questionnaire with multiple-choice and asked to identify the odor corresponding to the odor strip for each smell. To complete the test, participants must indicate if there is any difficulty with smells (yes/no) to examine awareness. The BSIT is a forced-choice test, in which the patient is educated to identify each odor, even if no particular smell is perceived. This test has good internal reliability as well as validity. This is why the BSIT is a well-suited test for evaluating odor identification alterations in older people of different backgrounds, demonstrating a sensitivity of 63% and specificity of 88% with an overall accuracy of 71% (42).
Extensive, detailed testing of olfactory function	
University of Pennsylvania Smell Identification Test (UPSIT)	The UPSIT is used to assess the individual's ability in detecting odors at a suprathreshold level, including 40 different smells. It consists in a quick self-administered test to quantitatively evaluate human olfaction (43). The UPSIT-40 has commonly been used in several countries as a diagnostic tool also in Parkinson Disease (PD) (44). Notably, UPSIT showed 82% sensitivity and 88.2% specificity (45, 46).
Barcelona Smell Test (BAST-24)	BAST-24 comprises 24 odors testing smell detection, identification, and forced choice. It is considered as a valid test to evaluate smell functioning [including the smell threshold, detection, memory, and identification (47)], in clinical practice. In addition, is can be useful to point out partial or total olfaction loss related to traumatic brain injury (48). It has been also validated in the Spanish and other Mediterranean populations.
Connecticut Chemosensory Clinical Research Center Test – (CCCRC)	The CCCRC test includes kits for odor detection and identification tests. The threshold evaluation is obtained using 9 serial dilutions of butanol in nanopore-deionized water. Each odor concentration is presented together with a control with water in a double-blind forced-choice paradigm. Given that, the threshold is described as the dilution at which the butanol bottle is correctly identified in 4 consecutive tests. If the water bottle is incorrectly indicated in less than 4 tests, the next higher concentration step is measured in a similar way (standard CCCRC test method). The CCCRC identification test comprises 7 smells (baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter, and soap). Three smells stimuli (ammonia, Vicks and VapoRub) are administered to test trigeminal nerve nasal performance but are not included in the final score calculation. In fact, the test score is composed by a maximum of 100 points, adding the threshold score (a maximum of 50 points) and identification score (a maximum of 50 points) CCCRC olfactory test is considered one of the most reliable tests for assessment of olfactory function (49).
T&T olfactometry	The first standardized olfactometer in Japan was fabricated in 1975, and it included five test odors and the averages of the threshold concentrations. Nowadays, the T & T Olfactometer is a widely used tool not only in many clinics and laboratories but also in many prefectures and cities. Notably, the T&T reliability values were found in detection ($r = 0.56$) and recognition ($r = 0.69$), indicating a relatively accuracy in assessing patients' olfactory ability (36, 48).
n-Butanol Threshold Test (n-BTt)	The n-BT allows the detection of the highest dilution of N-butanol correctly identified four times by the test subject. The patients are forced to choose between two options: odor or odorless. The identification test comprises 10 smells presented in pots and the subject is asked to pick them from a list of 20 proposals (50). This test is administered in clinical practice, to assess olfactory dysfunction in traumatic brain injury subjects
Olfactometer Test (O-Test)	Olfactometry is a precise testing method. Olfactory function can be tested through blast (Elsberg-Levy) olfactometry, a widely used tool to measure the olfactory threshold (34).T.his olfactometer determines the entry of a stream of air with a specific volume containing odorant molecules directly in the nasal cavity. The patient simultaneously presses the other nasal passage with his finger by pressing on the nostrils and shortly holding their breath. A clamp is located on the tube feeding air into the nasal cavity (51, 52).
Complementary/Additional measures	
Sino-Nasal Outcome Test (SNOT-22)	SNOT-22 is a questionnaire used to assess QoL in TBI patients. As the score increases, the QoL gets worse (Total score range: 0–110). SNOT- 22 may provide a valid instrument for the subjective QoL assessment of patients affected by PTOD (53). In particular, it has a sensitivity and specificity of 91.49 and 69.23%, respectively. Psychometric analyses support the accuracy, sensitivity, and specificity of the nasal domains of SNOT-22 to assess the impact on quality of life of the population with OD (54).

(Continued)

TABLE 1 (Continued)

Subjective olfactory measures	Description
Diagnostic Assessment of Nonverbal Affect 2-Adult Faces (DANVA2-AF)	The Diagnostic Assessment of Nonverbal Affect 2–Adult Faces (DANVA2-AF) is often administered to evaluate facial affect recognition. Twenty-four faces are showed on computer screens and patients had to pick emotion (happy, sad, angry and fearful) from a list. Faces equally varied in sex, race, and expression intensity. Faces are showed on the screen for 15 s. Test scores range from 0 to 24 (55). The DANVA-2 presents some psychometric properties: internal consistency for adult and child faces subtests were 0.70 and 0.75, respectively. While test–retest reliability ranged from 0.78 to 0.84 (56).
Emotional Inference from Stories Test (EIST)	The Emotional Inference from Stories Test (EIST) consists in a set of 12 short tales, and it is administered to evaluate a participant's ability to infer emotions from context. Each tale is presented one at a time on a computer with audio and video feedback. After that, patients had to answer a question about the character's predominant emotion from a list of the following 4 options: happy, sad, angry, and fearful. They were not able to refer to the story to answer the question. Test scores range from 0 to 12. The EIST appears to be more sensitive to deficits in emotion inferencing abilities, as evidenced in the significantly lower scores on each version by people with TBI compared to healthy population (57).
Diagnostic Assessment of Nonverbal Affect 2-Adult Paralanguage (DANVA2-AP)	The Diagnostic Assessment of Nonverbal Affect 2-Adult Paralanguage (DANVA2-AP) is often administered to assess vocal affect recognition. One sentence that is neutral in content is presented orally 24 times with varying paralinguistic cues expressing different emotions. Participants should select the expressed emotion from a list of the following: happy, sad, angry, and fearful. The test scores range from 0 to 24. Notably, the test–retest reliability ranges from 0.73 to 0.93 (58).
Interpersonal Reactivity Index (IRI)	Empathy can be tested with the Interpersonal Reactivity Index (IRI), which tests total empathy and 4 empathy subtypes, using a self-report scale: perspective-taking (PT), empathic concern (EC), fantasy scale (FS), and personal distress (PD). The IRI has 28 items designed to capture these components of empathy. Participants had to estimate how well each statement described them through 5-point Likert scale. Total empathy scores range from 0 to 112. The psychometric properties of IRI include test–retest reliability and internal reliability (59). In adult population test–retest reliabilities of IRI ranged from 0.61 to 0.79 for males and 0.62 to 0.81 for females (60).

UPSIT, University of Pennsylvania Smell Identification Test; BAST-24, Barcelona Smell Test; SNOT-22, Sino-Nasal Outcome Test; VAS, Visual Analog Scale (0–100 mm); n-BTt, n-Butanol Threshold Test; SStt, Snap and Sniff Threshold Test; OTest, Olfactometric Test; SS, Sniffin' Sticks; CCCRC, Connecticut Chemosensory Clinical Research Center Test; T&T, olfactometry; BSIT, Brief Smell Identification Test; DANVA2-AF, Diagnostic Assessment of Nonverbal Affect 2-Adult Faces; DANVA2-AP, Diagnostic Assessment of Nonverbal Affect 2-Adult Paralanguage; EIST, Emotional Inference from Stories Test; IRI, Interpersonal Reactivity Index.

the degree of axon degeneration in human olfactory mucosa correlates with olfactory function (82).

4. Olfactory training: from the conventional to innovative approaches

Olfactory training (OT) can be considered a non-pharmacological and non-invasive treatment option for patients affected by TBI with consequences in olfactory functioning (83), but also in individuals with signs of depression (84), neurodegenerative diseases such as Parkinson's disease and older adults (85). Generally, OT consists in the administration of specific fragrances (i.e., floral, fruity, and more intense aromas such as eucalyptus) inhaled, which can stimulate the olfactory nerve and promote neuroplasticity (Figure 2).

Recently, a meta-analysis (86) found that OT was effective in 36.31% of PTOD patients who achieved clinically significant results after 8 months of training, while 27% of patients experienced spontaneous recovery of olfaction. In fact, OT could promote olfactory function through top-down (central) rather than bottom-up (peripheral) processes, as confirmed by Pellegrino et al. (87) and Konstantinidis et al. (88) applied to their patients a systematic OT for sixteen weeks, twice daily (in the morning and in the evening) and using four different odors, including phenyl ethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves); each odor was administered for ten seconds, with the same time interval of ten seconds between smells. They found that OT increased the identification and discrimination of olfactory functions in TBI patients, with positive effects also in cognitive functions. However, Jiang et al. (89) found that the administration of phenyl ethyl alcohol during OT produced improvements in olfactory thresholds in 23% of patients affected by post-traumatic anosmia but did not improve the odor identification ability. Using the Konstantinidis's protocol (88), some authors suggested that the training is based on modulation of the regeneration processes linked to the repeated exposure to an odor, involving olfactory bulb and brain connectivity (90, 91).

Rezaeyan et al. (92), indeed, introduced a modified OT (Figure 1) stimulating the olfactory receptors with a variety of odorants over a certain period. The olfactory training was performed using four different packages including: (1) rose, lemon, thyme, and eucalyptus for the first month; (2) narcissus, strawberry, cardamom, and peppermint for the second month; (3) saffron, banana, cinnamon and garlic for the third month; (4) blossom, orange, vanilla and vinegar for the fourth month and led to positive results. It seems that the effectiveness of both OT, traditional and modified, depends on improved cognitive processing of olfactory information and increased attention paid to odors, supporting greater involvement of the CNS (93).

Laing et al. have described a rehabilitative method founded on the paradigm employed by Zelano et al., in which a neural representation of an odor is recalled from olfactory memory. In fact, the visual sighting of a food and imaging the food odor could activate the posterior piriform cortex that may allow a subject to perceive and identify the odor using central mechanisms only (94). Nevertheless, the effects of OT on neural structural changes due to the close connection between brain structure and olfactory function remains an unsolved question (95). For these reasons, more research is needed

TABLE 2 Description of the main objective measures to evaluate olfaction in patients affected by TBI.

Objective measures	Description
Electroencephalography (EEG)	Electroencephalography (EEG) in olfactory-bulb-associated areas can be used to assess the electrical activity changes in olfactory-bulb-associated brain regions (58). To investigate these areas high density EEG, using at least 128 channels, is fundamental.
Single Photon Emission Computed Tomography Image (SPECT-MRI) with Nasal Thallium-201	SPECT-MRI Image with Nasal Thallium-201 administration is a new assessment tool for olfactory nerve damage. This instrument is particularly useful to scan the olfactory nerve connectivity impairments in patients with olfactory alterations (61).
Event-related potentials (OERPs) Electrophysiological technique	An objective electrophysiological examination, using event-related potentials, to identify the olfactory defects (Elsberg Levy method – cortical evoked potentials) and to observe changes in olfactory functions (57).

EEG, Electroencephalography; SPECT-MRI Image with Nasal Thallium-201, Single Photon Emission Computed Tomography Image with Nasal Thallium-201; OERPs, Olfactory Event-related potentials.

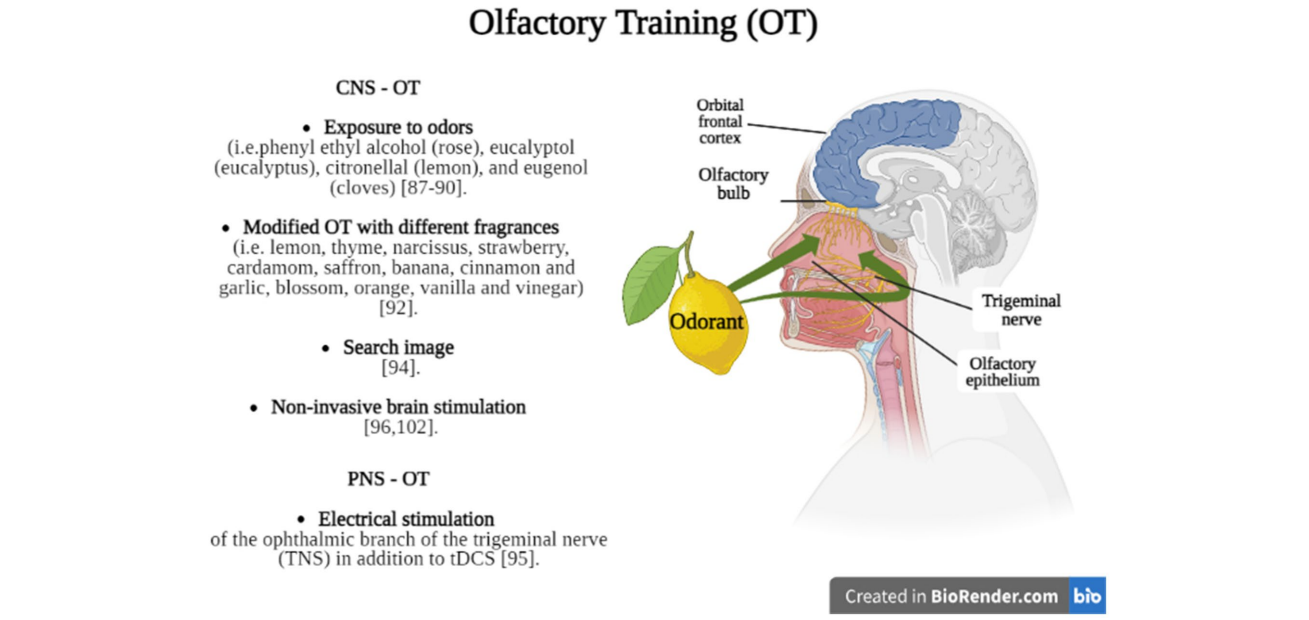

FIGURE 2
Briefly shows the main OT methods divided into techniques which stimulate olfactory function through CNS (CNS – OT) or PNS (PNS – OT) stimulation. Created in BioRender.com.

to clarify the optimal odor concentration, training duration, frequency, and the most suitable population for OT to better understand mechanisms underlying the recovery processes.

The olfactory nerve can also play a key role in such plastic and regenerative processes (96). Indeed, it has been shown that neurostimulation (about thirty minutes), delivered to the ophthalmic branch of the trigeminal nerve through trigeminal nerve stimulation and transcranial direct current stimulation, significantly improved the olfactory performance to guaiacol, an odorant involved in the activation of intranasal trigeminal circuit. In this way, both methods may induce persistent modulation changes through a direct activation of the trigeminal nerve. On the other hand, these neuromodulator effects may be driven *via* activation of distal secondary olfactory cortex structures, such as the orbitofrontal cortex which is highly associated with processing of odor learning and memory. In fact, non-invasive brain stimulation (NIBS) is considered an emerging and promising approach to induce long-lasting neuroplastic changes through electrical and/or magnetic energy. According to Hara et al. (97), the combined use of NIBS with rehabilitation could enhance a positive synergic effect, promoting not only modulation of neural connections, but also functional re-learning in post-TBI patients. However, the use of NIBS in the treatment of PTOD is an issue that deserves to be investigated.

5. Discussion

Olfactory dysfunction is an underestimated and challenging issue in TBI that worsens patients' QoL, not only in eating and enjoyment of food, but also in hazard avoidance (gas leaks, smoke detection, chemical vapors, and rotten food). Our review suggests that PTOD is commonly associated with cognitive and neuropsychiatric sequelae in TBI patients due to OFC damage, and some authors reported that OD is also linked to the neurodegenerative pathology. Then, it could be considered as a clinical marker of neurodegeneration likewise other more direct clinical, biological and neuroimaging markers. For this reason, an early assessment of olfactive function should be implemented

in clinical practice, especially when dealing with TBI, and this is why a comprehensive review on this issue is of utmost importance. In fact, it seems that olfactory testing, especially in the acute phase, could be useful as a screening tool for long-term outcomes, including mood symptoms. According to Logan et al., there is a bidirectional correlation between OD and depression, due to reduced input to the olfactory bulb and the consequential lower levels of neurotransmitter concentration, leading to the potential disturbance of emotional functioning (98).

PTOD is also related to other neuropsychiatric sequelae, including anxiety which affects odor thresholds, identification and discrimination of different smells. It seems that the amygdala and the OFC are both involved in anxious states and in the olfactory functioning (99). OD is also associated with impulsivity probably because OFC, is involved in both olfactory neural pathways and the regulation and inhibition of behavior (100).

Moreover, it has been shown that detection of olfactory abnormalities may be related to affect and empathy deficits (19), and this could be due to a common dopaminergic pathway dysfunction. Then, addressing OD and the related cognitive/behavioral dysfunction may be of help in better manage the rehabilitation of patients with TBI. Clinicians have a wide range of PTOD assessment methods, both subjective and objective, although it is not always easy to administer the right test or measure. The Sniffin' Test, UPSIT and CCCRC are the most used in clinical practice for their rapidity and cost convenience. Despite their short duration, there are some limitations related to learning effects due to repeated testing, and the low resolution in terms of detecting changes. In detail, the CCCRC and the BAST-24 provide verbal odor identification which is strictly dependent on language function and cognition (101). This is why patients are exposed to a pre-selected list of odor descriptors without which there would be no reliable clinical results. However, the BAST-24 is particularly useful to detect not only olfactory changes, but also neurobehavioral disorders (i.e., eating) (100).

OERPs are instead more accurate to detect changes in olfactory function, despite their limited availability in standard health care and the high cost of administration. Nevertheless, objective examinations are particularly useful when level of cognition is too impaired or when subjects may exaggerate the smell deficit for a secondary gain or for other medico-legal reasons. In addition, OERPs allow to understand the site of damage: loss of smell without loss of OERPs suggest peripheral nerve lesions, while a reduction/absence of OERPs indicates damage to central olfactory system (72). Another important issue to consider is the best way to manage PTOD, although it is still an underestimated problem. Currently, evidence supports the use of topical corticosteroids that allow neuronal recovery following olfactory nerve transection through the reduction of the inflammatory reaction and decrease of glial scar formation (101). This may explain why corticosteroids combined with OT are more effective (102). Other medications to treat olfactory loss include supplementation with alpha-lipoic acid, vitamin A and omega-3 for their neurodegenerative potential and antioxidant properties. Other promising treatments are related to the administration of the experimental N-acetylcysteine (100 mg/kg twice daily) after acute olfactory neuronal injury in animal models, since it reduces neural loss in the olfactory bulb (103). In fact, the neuroprotective effect of this medication could provide clinical benefit also in the TBI population. OT has been introduced in patients' care despite the lack of specific recommendations; moreover, its role in stimulating central or peripheral components of the olfactory system is mostly unknown. For this reason, the real effectiveness of OT remains a challenge, although it could be considered a good option to manage this growing and important problem. According to Turner et al. (104), a higher quality of evidence is needed with respect to patient populations, protocols, and outcome measures. Recently, researchers have studied the role of emerging approaches, including the use of NIBS that could boost neuroplasticity, further potentiating the OT after-effects (105–107). However, the lack of conclusive evidence does not allow to recommend this therapeutic approach in terms of efficacy. Another treatment for olfactory dysfunction is the use of platelet-rich-plasma which is derived from blood's patient with pro-regenerative properties (108). Nevertheless, larger studies are needed to understand if it can be adaptable also in TBI patients. Finally, the traditional Chinese acupuncture (109), used for various medical conditions, was proven effective in post-viral infection patients who were refractory to other treatments, including OT, oral steroids and supplementation. Although the reporting information in this review followed the PRISMA guidelines to reduce bias, there are some limitations to acknowledge. Since we included only English papers, some studies may have been excluded based on the language criteria. In addition, we did not provide any statistical analysis for each study included because of our intention was to describe the most used tools and methods to assess olfactory function in PTOD and its rehabilitative approach, since an international consensus about a gold-standard does not exist yet.

6. Conclusion

In conclusion, an early assessment of olfactory sense, considering also its correlation with cognitive functioning, is recommended in clinical practice and especially in the rehabilitation of patients with TBI. Although no clear evidence exists on the best treatment option, OT could be considered a valuable and effective tool to promote neuroplastic processes and improve OD following TBI. Further research is needed to investigate the promising role of OT coupled to other emerging training methods in the management of patients with TBI and olfactory loss and/or alterations.

Author contributions

MB, RC, and RL: conceptualization and investigation. MB and RL: methodology, data curation, and writing—original draft preparation. MB and CR: software. RL, MB, CR, AQ, and RC: validation and visualization. AQ: resources and funding acquisition. RC: writing—review and editing and supervision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Frasnelli J, Laguë-Beauvais M, LeBlanc J, Alturki AY, Champoux MC, Couturier C, et al. Olfactory function in acute traumatic brain injury. *Clin Neurol Neurosurg*. (2016) 140:68–72. doi: 10.1016/j.clineuro.2015.11.013

2. Costanzo RM, Miwa T. Post traumatic olfactory loss. *Adv Otorhinolaryngol*. (2006) 63:99–107. doi: 10.1159/000093753

3. Bratt M, Skandsen T, Hummel T, Moen KG, Vik A, Nordgård S, et al. Frequency and prognostic factors of olfactory dysfunction after traumatic brain injury. *Brain Inj*. (2018) 32:1021–7. doi: 10.1080/02699052.2018.1469043

4. Howell J, Costanzo RM, Reiter ER. Head trauma and olfactory function. *World J Otorhinolaryngol Head Neck Surg*. (2018) 4:39–45. doi: 10.1016/j.wjorl.2018.02.001

5. Costanzo RM, Reiter RJ, Yelverton JC. Smell and taste In: ND Zasler, DI Katz and RD Zafonte, editors. *Brain injury medicine: Principles and practice*. New York, NY: Demos (2012). 794–808.

6. Marin C, Langdon C, Alobid I, Mullol J. Olfactory dysfunction in traumatic brain injury: the role of neurogenesis. *Curr Allergy Asthma Rep*. (2020) 20:55. doi: 10.1007/s11882-020-00949-x

7. Wood RL, Worthington A. Neurobehavioral abnormalities associated with executive dysfunction after traumatic brain injury. *Front Behav Neurosci*. (2017) 11:195. doi: 10.3389/fnbeh.2017.00195

8. Langdon C, Laxe S, Lehrer E, Berenguer J, Alobid I, Quintó L, et al. Loss of smell in patients with traumatic brain injury is associated with neuropsychiatric behavioral alterations. *Brain Inj*. (2021) 35:1418–24. doi: 10.1080/02699052.2021.1972447

9. Ahmedy F, Mazlan M, Danaee M, Abu Bakar MZ. Post-traumatic brain injury olfactory dysfunction: factors influencing quality of life. *Eur Arch Otorhinolaryngol*. (2020) 277:1343–51. doi: 10.1007/s00405-020-05823-0

10. Drummond M, Douglas J, Olver J. 'If I haven't got any smell … I'm out of work': consequences of olfactory impairment following traumatic brain injury. *Brain Inj*. (2013) 27:332–45. doi: 10.3109/02699052.2012.750743

11. Schofield PW, Doty RL. The influence of head injury on olfactory and gustatory function. *Handb Clin Neurol*. (2019) 164:409–29. doi: 10.1016/B978-0-444-63855-7.00023-X

12. Hähner A, Hummel T. Classic Phantosmia. *Dtsch Arztebl Int*. (2020) 117:689. doi: 10.3238/arztebl.2020.0689a

13. Caminiti F, Ciurleo R, Bramanti P, Marino S. Persistent anosmia in a traumatic brain injury patient: role of orbitofrontal cortex. *Brain Inj*. (2013) 27:1715–8. doi: 10.3109/02699052.2013.823667

14. Singh R, Humphries T, Mason S, Lecky F, Dawson J, Sinha S. The incidence of anosmia after traumatic brain injury: the SHEFBIT cohort. *Brain Inj*. (2018) 32:1122–8. doi: 10.1080/02699052.2018.1483028

15. Sigurdardottir S, Andelic N, Skandsen T, Anke A, Roe C, Holthe OO, et al. Olfactory identification and its relationship to executive functions, memory, and disability one year after severe traumatic brain injury. *Neuropsychology*. (2016) 30:98–108. doi: 10.1037/neu0000206

16. Alderfer BS, Arciniegas D, Silver JM. Treatment of depression following traumatic brain injury. *J Head Trauma Rehabil*. (2005) 20:544–62. doi: 10.1097/00001199-200511000-00006

17. Rolls ET, Cheng W, Feng J. The orbitofrontal cortex: reward, emotion and depression. *Brain Commun*. (2020) 2:fcaa196. doi: 10.1093/braincomms/fcaa196

18. Osborne-Crowley K, McDonald S. Hyposmia, not emotion perception, is associated with psychosocial outcome after severe traumatic brain injury. *Neuropsychology*. (2016) 30:820–9. doi: 10.1037/neu0000293

19. Neumann D, Zupan B, Babbage DR, Radnovich AJ, Tomita M, Hammond F, et al. Affect recognition, empathy, and dysosmia after traumatic brain injury. *Arch Phys Med Rehabil*. (2012) 93:1414–20. doi: 10.1016/j.apmr.2012.03.009

20. Lecuyer Giguere F, Jobin B, Robert J, Bastien L, Giguère JF, De Beaumont L, et al. Early parosmia signs and affective states predicts depression and anxiety symptoms six months after a mild traumatic brain injury. *Chem Senses*. (2020):bjaa037. doi: 10.1093/chemse/bjaa037

21. Ciurleo R, De Salvo S, Bonanno L, Marino S, Bramanti P, Caminiti F. Parosmia and neurological disorders: a neglected association. *Front Neurol*. (2020) 11:543275. doi: 10.3389/fneur.2020.543275

22. Terpstra AR, Girard TA, Colella B, Green REA. Higher anxiety symptoms predict progressive hippocampal atrophy in the chronic stages of moderate to severe traumatic brain injury. *Neurorehabil Neural Repair*. (2017) 31:1063–71. doi: 10.1177/1545968317736817

23. Hudak A, Warner M, Marquez de la Plata C, Moore C, Harper C, Diaz-Arrastia R. Brain morphometry changes and depressive symptoms after traumatic brain injury. *Psychiatry Res*. (2011) 191:160–5. doi: 10.1016/j.pscychresns.2010.10.003

24. Bainbridge KE, Byrd-Clark D, Leopold D. Factors associated with phantom odor perception among US adults: findings from the National Health and nutrition examination survey. JAMA. *Otolaryngol Head Neck Surg*. (2018) 144:807–14. doi: 10.1001/jamaoto.2018.1446

25. Landis BN, Reden J, Haehner A. Idiopathic phantosmia: outcome and clinical significance. *ORL J Otorhinolaryngol Relat Spec*. (2010) 72:252–5. doi: 10.1159/000317024

26. Leopold D. Distortion of olfactory perception: diagnosis and treatment. *Chem Senses*. (2002) 27:611–5. doi: 10.1093/chemse/27.7.611

27. Jafari A, Holbrook EH. Therapies for olfactory dysfunction – an update. *Curr Allergy Asthma Rep*. (2022) 22:21–8. doi: 10.1007/s11882-022-01028-z

28. Helman SN, Adler J, Jafari A, Bennett S, Vuncannon JR, Cozart AC, et al. Treatment strategies for postviral olfactory dysfunction: a systematic review. *Allergy Asthma Proc*. (2022) 43:96–105. doi: 10.2500/aap.2022.43.210107

29. Welge-Lüssen A, Hilgenfeld A, Meusel T, Hummel T. Longterm follow-up of posttraumatic olfactory disorders. *Rhinology*. (2012, 2012) 50:67–72. doi: 10.4193/Rhino11.141

30. AbdelBari Mattar M, El Adle H. Prognostic factors for olfactory dysfunction in adult mild head trauma. *World Neurosurg*. (2020) 141:e545–52. doi: 10.1016/j.wneu.2020.05.232

31. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. *Rhinology*. (2017) 55:17–26. doi: 10.4193/Rhino16.195

32. Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Constantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction. *Laryngoscope*. (2013) 123:E85–90. doi: 10.1002/lary.24390

33. Su B, Bleier B, Wei Y, Wu D. Clinical implications of psychophysical olfactory testing: assessment, diagnosis, and treatment outcome. *Front Neuro Sci*. (2021) 15:646956. doi: 10.3389/fnins.2021.646956

34. Limphaibool N, Iwanowski P, Kozubski W, Swidziński T, Frankowska A, Kamińska I, et al. Subjective and objective assessments of post-traumatic olfactory dysfunction. *Front Neurol*. (2020) 11:970. doi: 10.3389/fneur.2020.00970

35. Çelik C, Güler H, Pehlivan M. Medicolegal aspect of loss of smell and olfactory event-related potentials. *Egypt J Forensic Sci*. (2022) 12:47. doi: 10.1186/s41935-022-00306-1

36. Červený K, Janoušková K, Vaněčková K, Zavázalová Š, Funda D, Astl J, et al. Olfactory evaluation in clinical medical practice. *J Clin Med*. (2022) 11:6628. doi: 10.3390/jcm11226628

37. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. *Rhinol Suppl*. (2017) 54:1–30. doi: 10.4193/Rhino16.248

38. Howell J, Costanzo RM, Reiter ER. Head trauma and olfactory function. *World J Otorhinolaryngol Head Neck Surg*. (2018) 4:39–45. doi: 10.1016/j.wjorl.2018.02.001

39. Haehner A, Mayer AM, Landis BN, Pournaras I, Lill K, Gudziol V, et al. High test-retest reliability of the extended version of the "Sniffin' sticks" test. *Chem Senses*. (2009) 34:705–11. doi: 10.1093/chemse/bjp057, PMID: 19759361

40. Delgado-Losada ML, Delgado-Lima AH, Bouhaben J. Spanish validation for olfactory function testing using the Sniffin' sticks olfactory test: threshold, discrimination, and identification. *Brain Sci*. (2020):10. doi: 10.3390/brainsci10120943

41. Suzuki Y, Yamamoto S, Umegaki H, Onishi J, Mogi N, Fujishiro H, et al. Smell identification test as an indicator for cognitive impairment in Alzheimer's disease. *Int J Geriatr Psychiatry*. (2004) 19:727–33. doi: 10.1002/gps.1161

42. Menon C, Westervelt HJ, Jahn DR, Dressel JA, O'Bryant SE. Normative performance on the brief smell identification test (BSIT) in a multi-ethnic bilingual cohort: a project FRONTIER study. *Clin Neuropsychol*. (2013) 27:946–61. doi: 10.1080/13854046.2013.796406

43. Picillo M, Pellecchia MT, Erro R, Amboni M, Vitale C, Iavarone A, et al. The use of University of Pennsylvania Smell Identification Test in the diagnosis of Parkinson's disease in Italy. *Neurol Sci*. (2014) 35:379–83. doi: 10.1007/s10072-013-1522-6

44. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys*. (1989) 45:381–4. doi: 10.3758/BF03210709

45. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. (1984) 32:e502. doi: 10.1016/0031-9384(84)90269-5

46. Morley JF, Cohen A, Silveira-Moriyama L, Lees AJ, Williams DR, Katzenschlager R, et al. Optimizing olfactory testing for the diagnosis of Parkinson's disease: item analysis of the university of Pennsylvania smell identification test. *NPJ Parkinson Dis*. (2018) 4:2. doi: 10.1038/s41531-017-0039-8

47. Cardesín A, Alobid I, Benítez P, Sierra E, de Haro J, Bernal-Sprekelsen M, et al. Barcelona smell test – 24 (BAST-24): validation and smell characteristics in the healthy Spanish population. *Rhinology*. (2006) 44:83–9.

48. Langdon C, Lehrer E, Berenguer J, Laxe S, Alobid I. Olfactory training in post-traumatic smell impairment: mild improvement in threshold performances: results from a randomized controlled trial. *J Neurotrauma*. (2018) 35:2641–52. doi: 10.1089/neu.2017.5230

49. Toledano A, González E, Onrubia TJ, Herráiz C, Mate MA, García M, et al. Test de olfato de Connecticut (CCCRC): valores en voluntarios sanos [the Connecticut Chemosensorial clinical research center olfaction test: values in healthy volunteers]. *Acta Otorrinolaringol Espanola*. (2003) 54:678–85. doi: 10.1016/S0001-6519(03)78467-2

50. Denzer MY, Gailer S, Kern DW, Schumm LP, Thuerauf N, Kornhuber J, et al. Quantitative validation of the n-butanol Sniffin' sticks threshold pens. *Chemosens Percept*. (2014) 7:91–101. doi: 10.1007/s12078-014-9168-1. Epub 2014 Apr 29

51. Schäfer L, Schriever VA, Croy I. Human olfactory dysfunction: causes and consequences. *Cell Tissue Res*. (2021) 383:569–79. doi: 10.1007/s00441-020-03381-9

52. Brattoli M, de Gennaro G, de Pinto V, Loiotile AD, Lovascio S, Penza M. Odour detection methods: olfactometry and chemical sensors. *Sensors (Basel)*. (2011) 11:5290–322. doi: 10.3390/s110505290

53. Gillett S, Hopkins C, Slack R, Browne JP. A pilot study of the SNOT 22 score in adults with no sinonasal disease. *Clin Otolaryngol*. (2009) 34:467–9. doi: 10.1111/j.1749-4486.2009.01975.x

54. La Mantia I, Ragusa M, Grigaliute E, Cocuzza S, Radulesco T, Calvo-Henriquez C, et al. Sensibility, specificity, and accuracy of the Sinonasal outcome test 8 (SNOT-8) in patients with chronic rhinosinusitis (CRS): a cross-sectional cohort study. *Eur Arch Otorhinolaryngol*. (2023) 280:3259–64. doi: 10.1007/s00405-023-07855-8

55. Nowicki S, Duke MP. Individual differences in the nonverbal communication of affect: the diagnostic analysis of nonverbal accuracy scale. *J Nonverb Behav*. (1994) 18:9–35. doi: 10.1007/BF02169077

56. Booth AJ, Rodgers JD, Volker MA, Lopata C, Thomeer ML. Psychometric characteristics of the DANVA-2 in high-functioning children with ASD. *J Autism Dev Disord*. (2019) 49:4147–58. doi: 10.1007/s10803-019-04130-w

57. Zupan B, Neumann D, Babbage DR, Willer B. Exploration of a new tool for assessing emotional inferencing after traumatic brain injury. *Brain Inj*. (2015) 29:877–87. doi: 10.3109/02699052.2015.1011233

58. Nowicki S Jr, Carton J. The measurement of emotional intensity from facial expressions: the DANVA FACES 2. *J Soc Psychol*. (1993) 133:749–50. doi: 10.1080/00224545.1993.9713934

59. Davis MH. A multidimensional approach to individual differences in empathy. *JSAS Catalog Select Doc Psychol*. (1980) 10:85.

60. Davis MH. Measuring individual differences in empathy: evidence for a multidimensional approach. *J Pers Soc Psychol*. (1983) 44:113–26. doi: 10.1037/0022-3514.44.1.113

61. Invitto S, Piraino G, Ciccarese V, Carmillo L, Caggiula M, Trianni G, et al. Potential role of OERP as an early marker of mild cognitive impairment. *Front Aging Neurosci*. (2018) 10:272. doi: 10.3389/fnagi.2018.00272

62. Humphries T, Singh R. Assessment of olfactory function after traumatic brain injury: comparison of single odour tool with detailed assessment tool. *Brain Inj*. (2018) 32:557–62. doi: 10.1080/02699052.2018.1434237

63. Hummel T, Sekinger B, Wolf S, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses*. (1997) 22:39–52. doi: 10.1093/chemse/22.1.39

64. Doty RL. Olfactory dysfunction and its measurement in the clinic. *World J Otorhinolaryngol Head Neck Surg*. (2015) 1:28–33. doi: 10.1016/j.wjorl.2015.09.007

65. Saltagi AK, Saltagi MZ, Nag AK, Wu AW, Higgins TS, Knisely A. Diagnosis of anosmia and Hyposmia: a systematic review. *Allergy Rhinol*. (2021) 12:21526567211026568. doi: 10.1177/21526567211026568

66. Renner B, Schreiber K. Olfactory and trigeminal interaction of menthol and nicotine in humans. *Exp Brain Res*. (2012) 219:13–26. doi: 10.1007/s00221-012-3063-2

67. Schofield PW, Moore TM, Gardner A. Traumatic brain injury and olfaction: a systematic review. *Front Neurol*. (2014) 5:5. doi: 10.3389/fneur.2014.00005

68. Sattin D, Bruzzone MG, Ferraro S, Nigri A, Leonardi M, Guido D. Coma research center, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy. Olfactory discrimination in disorders of consciousness: a new sniff protocol. *Brain Behav*. (2019) 9:e01273. doi: 10.1002/brb3.1273

69. Frank RA, Dulay MF, Gesteland RC. Assessment of the sniff magnitude test as a clinical test of olfactory function. *Physiol Behav*. (2003) 78:195–204. doi: 10.1016/S0031-9384(02)00965-4

70. Kobal G, Palisch K, Wolf SR, Meyer ED, Hüttenbrink KB, Roscher S, et al. A threshold-like measure for the assessment of olfactory sensitivity: the "random" procedure. *Eur Arch Otorhinolaryngol*. (2001) 258:168–72. doi: 10.1007/s004050100328

71. Murata Y, Okutani F, Nakahira M, Ushida T, Ikemoto T, Yokoe I, et al. Effects of olfactory stimulation with isovaleric acid on brain activation in informed and naı¨ve conditions: a functional MRI study. *Auris Nasus Larynx*. (2007) 34:465–9. doi: 10.1016/j.anl.2007.01.014

72. Gudziol H, Guntinas-Lichius O. Electrophysiologic assessment of olfactory and gustatory function. *Handb Clin Neurol*. (2019) 164:247–62. doi: 10.1016/B978-0-444-63855-7.00016-2

73. Caminiti F, De Salvo S, De Cola MC, Russo M, Bramanti P, Marino S. Detection of olfactory dysfunction using olfactory event related potentials in young patients with multiple sclerosis. *PLoS One*. (2014) 9:e103151. doi: 10.1371/journal.pone.0103151

74. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA*. (2002) 288:2307–12. doi: 10.1001/jama.288.18.2307

75. Huttenbrink KB, Hummel T, Berg D, Gasser T, Hähner A. Olfactory dysfunction: common in later life and early warning of neurodegenerative disease. *Dtsch Arztebl Int*. (2013) 110:1. doi: 10.3238/arztebl.2013.0001

76. Marin C, Vilas D, Langdon C, Alobid I, López-Chacón M, Haehner A, et al. Olfactory dysfunction in neurodegenerative diseases. *Curr Allergy Asthma Rep*. (2018) 18:42. doi: 10.1007/s11882-018-0796-4

77. Haehner A, Boesveldt S, Berendse HW, Mackay-Sim A, Fleischmann J, Silburn PA, et al. Hummel T prevalence of smell loss in Parkinson's disease a multicenter study. *Parkinsonism Relat Disord*. (2009) 15:490–4. doi: 10.1016/j.parkreldis.2008.12.005

78. Doty RL, Kamath V. The influences of age on olfaction: a review. *Front Psychol*. (2014) 5:20. doi: 10.3389/fpsyg.2014.00020

79. Mobley AS, Rodriguez-Gil DJIF, Greer CA. Aging in the olfactory system. *Trends Neurosci*. (2013) 37:77–84. doi: 10.1016/j.tins.2013.11.004

80. Croy I, Hummel T. Olfaction as a marker for depression. *J Neurol*. (2017) 264:631–8. doi: 10.1007/s00415-016-8227-8

81. Hummel T, Podlesek D. Clinical assessment of olfactory function. *Chem Senses*. (2021) 46:bjab053. doi: 10.1093/chemse/bjab053

82. Shiga H, Taki J, Washiyama K, Yamamoto J, Kinase S, Okuda K, et al. Miwa T Assessment of olfactory nerve by SPECT-MRI image with nasal thallium-201 administration in patients with olfactory impairments in comparison to healthy volunteers. *PLoS One*. (2013) 8:e57671. doi: 10.1371/journal.pone.0057671, PMID: 23469046

83. Jafari A, Holbrook EH. Therapies for olfactory dysfunction – an update. *Curr Allergy Asthma Rep*. (2022) 22:21–8. doi: 10.1007/s11882-022-01028-z

84. Eliyan Y, Wroblewski KE, McClintock MK, Pinto JM. Olfactory dysfunction predicts the development of depression in older US adults. *Chem Senses*. (2020) 46:bjaa075. doi: 10.1093/chemse/bjaa075

85. Haehner A, Hummel T, Reichmann H. Olfactory loss in Parkinson's disease. *Parkinson Dis*. (2011):450939. doi: 10.4061/2011/450939

86. Huang T, Wei Y, Wu D. Effects of olfactory training on posttraumatic olfactory dysfunction: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. (2021) 11:1102–12. doi: 10.1002/alr.22758

87. Pellegrino R, Han P, Reither N, Hummel T. Effectiveness of olfactory training on different severities of posttraumatic loss of smell. *Laryngoscope*. (2019) 129:1737–43. doi: 10.1002/lary.27832

88. Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Constantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction. *Laryngoscope*. (2013) 123:E85–90. doi: 10.1002/lary.24390

89. Jiang RS, Twu CW, Liang KL. The effect of olfactory training on odor identification in patients with traumatic anosmia. *Int Forum Allergy Rhinol*. (2019) 9:1244–51. doi: 10.1002/alr.22409

90. Altundag A, Saatci O, Kandemirli SG, Sanli D, Duz OA, Sanli AN, et al. Imaging features to predict response to olfactory training in post-traumatic olfactory dysfunction. *Laryngoscope*. (2021) 131:E2243–50. doi: 10.1002/lary.29392

91. Chang Y. Reorganization and plastic changes of the human brain associated with skill learning and expertise. *Front Hum Neurosci*. (2014) 8:35. doi: 10.3389/fnhum.2014.00035

92. Rezaeyan A, Asadi S, Kamrava SK, Khoei S, Zare-Sadeghi A. Reorganizing brain structure through olfactory training in post-traumatic smell impairment: an MRI study. *J Neuroradiol*. (2022) 49:333–42. doi: 10.1016/j.neurad.2021.04.035

93. Hu B, Zhang J, Gong M, Deng Y, Cao Y, Xiang Y. Ye D Research Progress of olfactory nerve regeneration mechanism and olfactory training. *Ther Clin Risk Manag*. (2022) 18:185–95. doi: 10.2147/TCRM.S354695, PMID: 35281777

94. Laing DG, Epps A, Jinks AL. Chemosensory loss during a traumatic brain injury suggests a central pathway for the rehabilitation of anosmia. *Chem Senses*. (2021) 46:bjab016. doi: 10.1093/chemse/bjab016

95. Badran BW, Gruber EM, O'Leary GH, Austelle CW, Huffman SM, Kahn AT, et al. Electrical stimulation of the trigeminal nerve improves olfaction in healthy individuals: a randomized, double-blind, sham-controlled trial. *Brain Stimul*. (2022) 15:761–8. doi: 10.1016/j.brs.2022.05.005

96. Henkin RI, Potolicchio SJ, Levy LM. Improvement in smell and taste dysfunction after repetitive transcranial magnetic stimulation. *Am J Otolaryngol*. (2011) 32:38–46. doi: 10.1016/j.amjoto.2009.10.001

97. Hara T, Shanmugalingam A, McIntyre A, Burhan AM. The effect of non-invasive brain stimulation (NIBS) on executive functioning, attention and memory in rehabilitation patients with traumatic brain injury: a systematic review. *Diagnostics*. (2021) 11:627. doi: 10.3390/diagnostics11040627

98. Logan M, Kapoor S, Peterson L, Oliveira M, Han DY. Mechanism of olfactory deficit in neurotrauma and its related affective distress: a narrative review. *World J Psychiatry*. (2021) 11:1259–66. doi: 10.5498/wjp.v11.i12.1259

99. Marin C, Alobid I, Fuentes M, López-Chacón M, Mullol J. Olfactory dysfunction in mental illness. *Curr Allergy Asthma Rep*. (2023) 23:153–64. doi: 10.1007/s11882-023-01068-z

100. Herman AM, Critchley H, Duka T. Decreased olfactory discrimination is associated with impulsivity in healthy volunteers. *Sci Rep*. (2018) 8:15584. doi: 10.1038/s41598-018-34056-9

101. Bratt M, Moen KG, Nordgård S, Helvik AS, Skandsen T. Treatment of posttraumatic olfactory dysfunction with corticosteroids and olfactory training. *Acta Otolaryngol*. (2020) 140:753–9. doi: 10.1080/00016489.2020.1767301

102. Vestito L, Mori L, Trompetto C, Bagnasco D, Canevari RF, Ponzano M, et al. Impact of tDCS on persistent COVID-19 olfactory dysfunction: a double-blind sham-controlled study. *J Neurol Neurosurg Psychiatry*. (2023) 94:87–8. doi: 10.1136/jnnp-2022-329162

103. Jafari A, Holbrook EH. Therapies for olfactory dysfunction – an update. *Curr Allergy Asthma Rep*. (2022) 22:21–8. doi: 10.1007/s11882-022-01028-z

104. Turner JH. Olfactory training: what is the evidence? *Int Forum Allergy Rhinol*. (2020) 10:1199–200. doi: 10.1002/alr.22681

105. Hedner M, Larsson M, Arnold N, Zucco G, Hummel T. Cognitive factors in odor detection, odor discrimination, and odor identification tasks. *J Clin Exp Neuropsychol*. (2010) 32:1062–7. doi: 10.1080/13803391003683070

106. Pekala K, Chandra RK, Turner JH. Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. *Int ForumAllergy Rhinol*. (2016) 6:299–307. doi: 10.1002/alr.21669

107. Goncalves S, Goldstein BJ. Acute N-acetylcysteine administration ameliorates loss of olfactory neurons following experimental injury in vivo. *Anat Rec*. (2020) 303:626–33. doi: 10.1002/ar.24066

108. Yan CH, Mundy DC, Patel ZM. The use of platelet-rich plasma in treatment of olfactory dysfunction: a pilot study. *Laryngoscope Investig Otolaryngol*. (2020) 5:187–93. doi: 10.1002/lio2.357

109. Dai Q, Pang Z, Yu H. Recovery of olfactory function in post viral olfactory dysfunction patients after acupuncture treatment. *Evid Based Complement Alternat Med*. (2016) 2016:4986034. doi: 10.1155/2016/4986034

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Advances in understanding the pathogenesis of post-traumatic epilepsy: a literature review

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Severe head trauma can lead to seizures. Persistent epileptic seizures and their progression are associated with the severity of trauma. Although case reports have revealed that early use of anti-seizure drugs after trauma can prevent epilepsy, clinical case–control studies have failed to confirm this phenomenon. To date, many brain trauma models have been used to study the correlation between post-traumatic seizures and related changes in neural circuit function. According to these studies, neuronal and glial responses are activated immediately after brain trauma, usually leading to significant cell loss in injured brain regions. Over time, long-term changes in neural circuit tissues, especially in the neocortex and hippocampus, lead to an imbalance between excitatory and inhibitory neurotransmission and an increased risk of spontaneous seizures. These changes include alterations in inhibitory interneurons and the formation of new, over-recurrent excitatory synaptic connections. In this study, we review the progress of research related to post-traumatic epilepsy to better understand the mechanisms underlying the initiation and development of post-traumatic seizures and to provide theoretical references for the clinical treatment of post-traumatic seizures.

KEYWORDS

post-traumatic epilepsy, ultrastructural, iron ion, free radicals, hippocampus

1. Introduction

Annually, approximately 64–74 million people suffer from traumatic brain injury (TBI) worldwide. The severity of TBI varies from mild to severe and may lead to post-traumatic syndromes, including depression and cognitive, emotional, and behavioral defects. TBI can increase the susceptibility to epilepsy and the incidence rate of epilepsy; this phenomenon is called post-traumatic epilepsy (PTE). However, in-depth studies on TBI, its biomarkers, and preventive measures are lacking. Furthermore, the exact mechanisms underlying the epileptic factors that may lead to PTE remain unclear.

Although the type and severity of damage can partially predict susceptibility to PTE, similar damage does not always lead to PTE (1). The location of the lesion may affect the risk of PTE because temporal lobe lesions after TBI are associated with a high incidence of early epilepsy and the longitudinal development of PTE (2). Penetrating lesions in the motor and parietal lobes are associated with an increased risk of PTE (3). Neuroinflammatory reactions occur rapidly. Based on increasing evidence from human and animal studies, neuroinflammatory reactions

play a role in the development of TBI (4). Generally, inflammatory factors, chemokines, and complement proteins are rapidly released after TBI. This immune response signal is composed of multiple cellular mediators that initiate acute-phase responses (5–11). Based on these signals, astrocytes and resident microglia are activated, proliferated, and migrated to the site of injury (12, 13). Peripheral immune cells also infiltrate the brain during the TBI response. Once this immune/neuroimmune response is activated to re-establish tissue homeostasis, these immune cells clear the debris and identify potential pathogenic signals. Although the strongest neuroinflammatory reaction occurs relatively early (within hours or days after injury), low levels of neural inflammation tend to persist for a long time (12–17). Acute, early, and chronic neural inflammations are also associated with epilepsy.

Some of the earliest neuropathologies indicated that progressive glial proliferation at the site of brain injury is a major factor in the formation of epileptic foci (3, 18). Increasing evidence supports the presence of glial scars and other neuroinflammatory mechanisms in PTE. Griffin and Mrak provided a platform that led to renewed attention to the mechanisms of neuroinflammation in neuropathological diseases. In this study, we provide a comprehensive review of neuroinflammation after TBI, focusing on the neuroinflammatory mechanisms that promote seizures, epilepsy, and PTE development. We also reviewed the experimental animal models used in PTE research, including those with neurophysiological and structural abnormalities, which are considered the basis for the increased tendency of spontaneous seizures in the injured brain. Notably, we focused on the modification of the damaged dentate gyrus synaptic network, which is related to the occurrence of PTE. The hippocampus is an important structural region involved in epilepsy. The dentate gyrus is particularly vulnerable and usually undergoes time-dependent structural reorganization. It is a widely used model system for changes in the synaptic circuits of cortical structures in epilepsy and is one of the best regions for characterizing changes in structure–function correlations after TBI.

Therefore, this review aimed to understand the mechanisms underlying epilepsy after TBI and to identify, develop, and validate therapeutic strategies to prevent PTE.

2. Epidemiological characteristics of PTE

Epilepsy is estimated to affect approximately 0.5–2% of the population. For patients who experienced a sudden head injury and/or were hospitalized for TBI, the incidence rate increased to approximately 5–7% (1, 18, 19). The higher the severity of the injury, the higher the risk of PTE, which is 10-fold higher in military patients with penetrating head trauma. In extreme cases, the incidence of PTE after a severe penetrating head injury is greater than 50% (20–22). Overall, up to 20% of symptomatic epilepsy cases are estimated to be caused by TBI, which is the most commonly known cause of seizures and epilepsy.

Although typical antiepileptic drugs such as levetiracetam and phenytoin sodium can effectively control early seizures that occur within the first week of TBI (23), these treatments do not necessarily improve the risk of PTE (24, 25). Approximately one-third of patients with PTE are resistant to antiepileptic therapy (25–27). Furthermore, the side effects of antiepileptic drugs are more severe in patients with PTE (28). Therefore, understanding the pre-epileptic mechanisms of TBI is crucial for diagnosing and treating PTE and improving the quality of life of these patients.

3. Brain structure and network-related mechanisms

Epilepsy is caused by an imbalance between excitation and inhibition in the central nervous system. Accordingly, factors that can increase the excitability or decrease the inhibition of the nervous system may induce epilepsy. The occurrence of PTE is no exception. Many studies have shown that axonal sprouting and the formation of new excitatory synaptic connections are key to the occurrence of PTE. In a pyramidal cell model (the classic PTE model), axon terminals emerged in the injured area, and GAP43, a protein related to axon terminals, was reactivated. On day three after injury, the expression of neurofilament proteins in the interneurons and vertebral cells began to increase and lasted for several weeks. Two to three weeks after injury, the frequency of excitatory postsynaptic currents in the cortical V-layer vertebral cells increases significantly and is accompanied by axon growth, axon branching, and an increased number of synapses (29–32). Using free glutamate laser scanning light stimulation technology, synaptic connections in the cortical disconnection model were observed. The number of excitatory connections of pyramidal cells in the epileptogenic focus and the amplitude of excitatory postsynaptic potentials recorded by electrophysiology increase significantly (33). These results confirm that the axon sprouting observed in the anatomy is new and functional and can be repeatedly overexcited to produce epileptiform discharges. Therefore, the enhancement of excitatory synapses plays an important role in the occurrence of PTE.

One of the most common causes of epilepsy after brain trauma is the formation of cortical scars (34, 35). The normal cortex was rich in the capillary network and leptomeningeal artery, whereas the middle area between the scar and normal cortex represented the anastomosis of the soft and dural arteries lacking capillaries. Damage to the myelin sheath and neurons and regeneration of neuronal synapses were also observed. The blood flow in the middle area is only 1/50 of that in normal brain tissue. Progressive gray matter atrophy, glial hyperplasia, and scar formation caused by ischemia pull surrounding tissues toward the center of the scar. Furthermore, vascular pulsation induces mechanical tension on the dendrites of the neurons in the middle area. Dendrites are highly sensitive to this tension, which causes the middle area to become the epileptic focus. Focal damage to the blood–brain barrier (BBB) is an initial factor in early post-traumatic seizures.

Both primary and secondary brain injuries caused by brain trauma can cause changes in the neurons themselves and their surrounding vascular tissues and glial cells and promote the excessive discharge of neuronal supersynchronization. The axons of normal neurons send out branches that inhibit the excitability of the neurons through a feedback circuit composed of interneurons. Collateral inhibition is most significant when excitability is abnormally elevated. When brain trauma occurs, these collaterals are first affected and lose their inhibitory effect, resulting in excessive excitation of neurons and triggering seizures (36). In addition, injury to superficial cortical dendrites during brain trauma can cause continuous depolarization

and discharge of local neurons, stimulate downstream neurons, and induce abnormal excitation, which together play a role in promoting seizures.

The term "epilepsy" refers to recurrent or unprovoked seizures. This process usually involves structural changes in the neural circuit owing to gradual neuronal damage and the "self-repair" mechanism, which develops during latency at different times, eventually ending in spontaneous, recurrent seizures. This process also has a variable latency period, indicating that a series of gradual cellular changes may be involved. Therefore, post-traumatic seizures in humans are usually classified according to the time after injury as immediate or impact-related (24 h after injury), early (1 week after injury), and late (1 week after injury). This classification model represents different pathophysiological processes. Understanding the epileptogenic process after TBI will help to clarify the importance of these cellular mechanisms in PTE and promote the development of new therapeutic targets. Trauma initiates a multidimensional cascade of cellular and molecular events with three types of overlapping responses in the brain: primary and secondary injuries and "self-repair" mechanisms. An important goal of studying the occurrence of PTE is to separate damage-induced cellular changes that promote epilepsy from compensatory and "self-repair" responses.

As shown in Figure 1, a series of cellular and molecular events after TBI involves three types of time-overlapping reactions in the brain: primary and secondary injury and the "self-repair" mechanism. In a multimodal magnetic resonance imaging (MRI) neuroimaging study evaluating brain trauma, PTE, and depression, the value of early quantitative MRI measurements of TBI in predicting traumatic epilepsy was explored. The degree of damage to the cortex, ipsilateral hippocampus, thalamus, and contralateral hippocampus in early TBI was found to be related to the occurrence of traumatic epilepsy, which does not occur immediately after trauma, but may occur within 3 weeks to 2 years after trauma. MRI includes susceptibility-weighted imaging (SWI) and diffusional kurtosis imaging (DKI) for the evaluation of microstructural changes in softening lesions and surrounding tissues after mild and moderate trauma and the possibility of epilepsy. SWI detects intracranial microbleeds with greater sensitivity, which is of great value for evaluating patients with mild brain injuries. Microbleeds in the frontal, parietal, and temporal lobes are associated with post-traumatic depression (25). Currently, it is difficult to determine whether depression during the post-traumatic rehabilitation stage is related to trauma. However, after traumatic epilepsy, the probability of depression in patients with epilepsy is relatively high, with epilepsy and associated depression affecting each other.

Magnetic resonance elastography (MRE) scans with an MRI pulse train to generate propagated sound waves and measurable tissue displacement are considered a particularly sensitive imaging tool that could increase the potential for early diagnosis of neurological diseases. It has been applied to many neurological diseases, such as multiple sclerosis, Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and amyotrophic lateral sclerosis. Regarding preclinical models of MRE, several studies have indicated its potential use in TBI. Using a TBI mouse model, longitudinal MRE studies showed that the elastic modulus of the injured brain tissue was higher than that of the contralateral hemisphere 1 h after injury. However, the elastic modulus decreased 1 day after injury and recovered in the brain tissue close to the contralateral hemisphere 7 days later. Although more preclinical and clinical validation is needed for this emerging model in the future, MRE technology holds promise for measuring the mechanical properties of the brain *in vivo* through noninvasive scans, with the potential to improve prognosis (37).

In humans, primary damage to the meninges and vasculature has been observed in the absence of significant brain damage after minor head trauma, as part of an ongoing mild TBI study evaluating MRI comparison studies of patients with mild craniocerebral injury who arrived at the emergency room within 48 h (38). Over 30 months, 142 patients with a baseline Glasgow coma score of 15 with significant loss

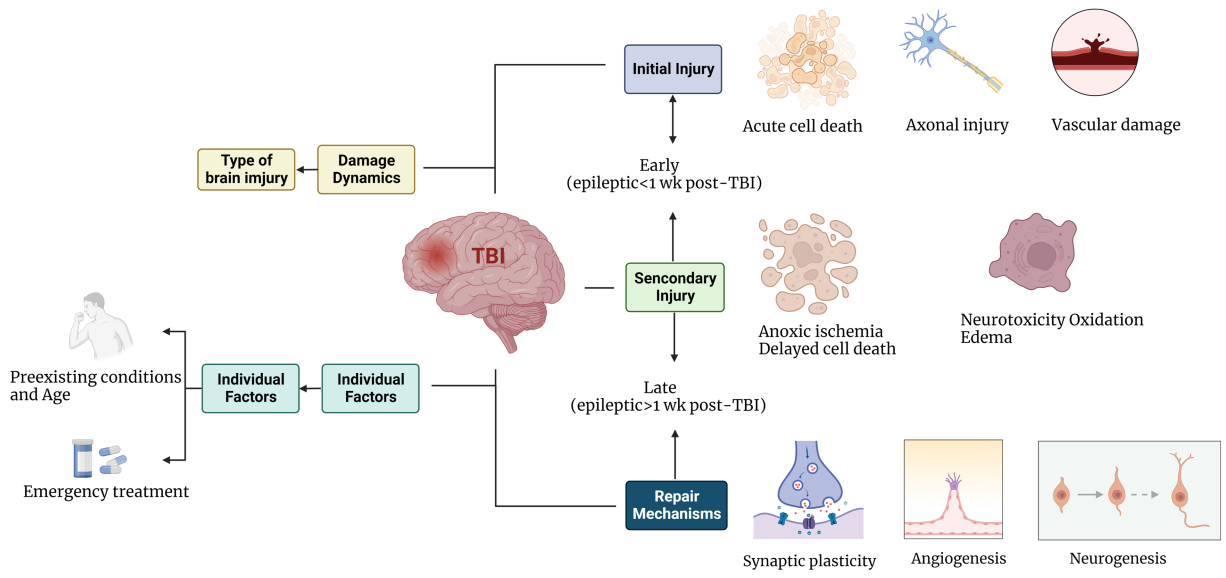

FIGURE 1
Progress of cellular events after brain trauma.

of consciousness or post-traumatic memory but no substantial injury on clinical computed tomography (CT) were enrolled. CT showed meningeal hemorrhage in 18 patients (12.7%), including subarachnoid hemorrhage in 13 patients (9.1%) and subdural hemorrhage in seven patients (4.9%). Focal enhancement of the meninges was observed on FLAIR MRI contrast imaging with no accompanying meningeal hemorrhage in 53 (36.9%) of 69 (48.6%) patients. This enhancement is the result of gadolinium contrast agent extravasation into spaces containing free fluids with a T1 relaxation time constant equal to the relaxation time of cerebrospinal fluid (CSF).

4. Epileptogenic mechanisms of inflammatory reaction

Epilepsy pathogenesis is closely associated with immune regulation. Immune cytokines play a key role in immune regulation and epilepsy. The inflammatory factors released by damaged neurons and glial cells initiate a vicious cycle of brain inflammation. Brain injury leads to the early activation of microglia and stimulates the production of cytokines and the expression of damage-associated molecular pattern-related receptors on the surface, leading to neuronal excitability. Molecules released by active glial cells and neurons increase the hyperexcitability of cells, and blood cells tend to migrate to the brain. Damage to the BBB leads to the infiltration of immune cells into the brain by blood-released proinflammatory factors and promotes excitotoxicity. Subsequently, the activated microglia release signals that bind to astrocyte receptors. Serum albumin-induced astrocyte activation can damage potassium and glutamate transporters. In addition, activated astrocytes release proinflammatory factors that aggravate neuronal hyperexcitability. These factors, either individually or in combination, can cause neurodegeneration. Cytokine-mediated crosstalk between astrocytes, microglia, and glial cells can induce neuronal overexcitation and death. In contrast, neuronal molecules such as heat shock protein (HSP60), high-mobility group box 1 (HMGB1), differentiation cluster 14 (CD14), chemokine (C-X3-C motif) ligand 1 (CX3CL1), and adenosine 5′-triphosphate (ATP) can activate microglia, leading to excitotoxicity. Monocytes and white blood cells release cytokines concurrently, creating an activation cycle that leads to the release of additional inflammatory molecules and triggers a cytokine storm in the brain. Macrophages release major histocompatibility complex II, complementary proteins, proinflammatory interleukins, inducible nitric oxide synthase (iNOS), transcription factors, microRNAs, and other molecules that cause neuronal excitotoxicity. These molecules promote neurodegeneration, initiate neuroinflammatory pathways, and reduce the seizure threshold. HSP60, heat shock protein; HMGB1, high-mobility group box 1; CD14, differentiation cluster 14; CX3CL1, chemokine (C-X3-C motif) ligand 1; ATP, adenosine 5′-triphosphate; inducible nitric oxide synthase. The BBB is typically damaged during brain trauma. One study found that the BBB was damaged in 82.4% of patients with epileptic seizures after brain trauma, which was 25% higher than that in patients without epileptic seizures. The abnormal EEG activity sites recorded in patients with PTE are usually consistent with brain regions with significant BBB damage. Moreover, continuously increased BBB permeability may be related to an increased frequency and degree of seizures in patients with PTE (39). Focal damage to the BBB is the initial factor in early post-traumatic seizures, followed by an abnormal excitability pattern in peripheral nerve seizures. Under normal circumstances, the BBB does not allow most blood-borne proteins from serum to enter the brain. Serum albumin is the most abundant protein in the blood. Normal individuals have low albumin levels in the CSF. After BBB damage caused by TBI, a sudden and continuous increase in albumin levels in the brain parenchyma can lead to seizures (40).

One study found that IL-1β levels are significantly increased in the CSF and serum of patients with TBI, which is related to the incidence of PTE (32). Recurrent seizures can lead to peripheral and central inflammation. Microglia and astrocytes release IL-1β during seizures and activate IL-1β receptor/Toll-like receptor signaling. Epilepsy induces IL-1 β release. The activation of adrenergic acids leads to many interrelated damage processes, including BBB damage. Further upregulation of signal transduction leads to an increase in extracellular potassium and glutamate levels, a decrease in the seizure threshold, and the loss of neurons. A peripheral inflammatory reaction appears in the center, leading to hyperfunctioning of the hypothalamus–pituitary–adrenal axis. Upon the activation of dioxygenase, the levels of toxic metabolites in the tryptophan metabolic pathway increase. Upon activation of the oxidation/nitrification stress pathway, oxygen and nitrogen free radicals increased. These reactions interacted with each other. Thereafter, the inflammation persists, effectively blocking any link in the reaction that may prevent the development of epilepsy-related depression (41). Thus, inflammation plays an important role in epilepsy. It can improve depression in patients with epilepsy by controlling inflammatory reactions.

5. Mechanisms underlying imbalances in neurotransmitter regulation

5.1. 5-HT

5-HT is a neurotransmitter that plays a role in central nervous system (CNS) infections and the peripheral nervous system, and several non-neuronal tissues are involved in membrane receptor interactions. The 5-HT system is also involved in the pathogenesis of epilepsy and neuropathic pain. The 5-HT1A, 5-HT2C, 5-HT3, and 5-HT7 receptors are involved in the occurrence and maintenance of epilepsy and changes in susceptibility to epilepsy. However, a 5-HT deficiency can cause seizures. Some antiepileptic drugs exert antiepileptic effects by increasing the levels of extracellular 5-HT receptors. The lack of 5-HT2 receptors significantly increases the risk of seizures. 5-HT2 receptors directly or indirectly control the excitability of neurons in the entire network structure by interacting with the monoamine neurotransmitters γ-aminobutyric acid (GABA) and glutamate (Glu) (42).

5.2. Glu

Glutamate is an excitatory neurotransmitter. Glu in and out of cells maintains a balance through the transport of protein channels between neurons and glial cells. After brain trauma, the extracellular Glu levels in the neocortex increase rapidly (43). Cell damage and

excessive synaptic activity after injury may increase the release of Glu from neurons and glial cells and reduce their reuptake. Thereafter, GLUergic receptors may become overexcited, eventually leading to neuronal damage or death, which is known as excitotoxicity (44, 45). Excitotoxicity is a major cause of various pathological changes following brain trauma. Brain trauma is a stress factor that can directly enhance the activity of glycinergic receptor channels and further aggravate the excitatory toxicity of brain tissue. A long-term imbalance in Glu levels will continue to affect the excitability of neurons, disrupt the balance between excitability and inhibition of the nervous system, and lead to epilepsy.

During seizures in patients with epilepsy, the expression of phospho-activated glutaminase increases in the hippocampus, converting glutamine to glutamic acid and thereby destroying the balance of glutamic acid in the body. Furthermore, the activity of glutamate dehydrogenase, which removes glutamic acid, decreases, leading to a decrease in glutamic acid degradation. Therefore, a disorder in glutamate metabolism in patients with epilepsy leads to increased glutamate synthesis and decreased glutamate degradation, which is related to intractable epilepsy (46).

In TBI, injured nerve cells consume energy and release glutamate and potassium ions from glial cells into the extracellular fluid, further aggravating the brain injury. Numerous studies have shown that Glu plays an important role in the pathophysiology of epilepsy and depression. First, the rapid metabolism of glutamate ensures that the postsynaptic target cells receive immediate stimulation to enable precise regulation. Second, high concentrations of extracellular Glu are associated with neurotoxicity. Therefore, the balance of glutamate function in the gap must be emphasized. At present, several lines of evidence, such as dysfunction of the glutamate transporter, abnormal concentrations of glutamate and GABA in the cerebral cortex, and the antidepressant effects of glutamate receptor antagonists, ultimately support the involvement of glutamate in the pathogenesis of depression (47).

In the study of neurotransmitter receptors related to the pathogenesis of epilepsy, kainate receptors belonging to the glutamic receptor family kainate (KA) are structural analogs of glutamate, an excitatory amino acid naturally extracted from seaweed. In animal models of KA-induced epilepsy, KA induces seizures and neuropathological damage in temporal lobe epilepsy, indicating that it is a potent toxin. The KAR family was identified by KAR subunit cloning and is composed of five receptor subunits: GLUR5, GLUR6, GLUR7, KA1, and KA2. The expression of GLUR5 was higher in patients with refractory epilepsy (48–50). The temporal cortex is also the lesion site of refractory temporal lobe epilepsy, but the main site of action of GLUR5 is not in the temporal cortex but in the hippocampus, the core lesion site of temporal lobe epilepsy. The hippocampus has been the dominant site for studying GLUR5. Our results further confirm that GLUR5 is involved in the pathogenesis of refractory temporal lobe epilepsy by acting on the hippocampus (51). High GLUR5 expression in patients with refractory epilepsy suggests its involvement in the pathogenesis of refractory epilepsy. Topiramate is the only antiepileptic drug that blocks the GLUR5 receptor. Topiramate has multiple mechanisms for blocking sodium channels, increasing GABA-mediated inhibition, blocking glutamate-mediated nerve excitability, and affecting chloride membrane transport and calcium channel blockade. Thus, it may act as an antiepileptic drug by selectively acting on GLUR5 receptors. It is necessary to further clarify the pathogenic relationship between GLUR5 and human refractory temporal lobe epilepsy and its pathological mechanism in refractory temporal lobe epilepsy, to provide a possible theoretical basis for the development of new antiepileptic drugs (52).

5.3. γ-aminobutyric acid

GABA is the main inhibitory neurotransmitter in the CNS, and its release from interneurons plays a role in regulating excitatory neurotransmission. Glutamine in astrocytes is transported to GABAergic neurons for conversion to glutamate, which is then immediately converted to GABA by glutamic acid decarboxylase. Glutamate, glutamine, and GABA depend on intermediates in the tricarboxylic acid cycle. Therefore, defects and inefficiencies in cellular energy metabolism, such as impaired tissue perfusion and increased neuronal metabolic demands after TBI, also lead to inadequate transmitter production. GABA is stored in presynaptic vesicles and released to postsynaptic terminals that may be located in dendritic processes, cell bodies, axons, or other axon terminals (53).

Upon release, GABA acts on the GABA-A and GABA-B receptors. GABA-A receptors are postsynaptic ion receptors containing at least 16 subunits. Different subtype combinations exhibit different physiological and pharmacological features. The combination of these isoforms depends on their colocalization at the neuronal membrane (54). The GABA-A subunits that have received the most attention in TBI studies are α1, γ2, α4, and δ1. These subunits contribute to the ability of GABA interneurons to modulate neuronal signaling through phase and tonic inhibition. These two inhibitors exhibit unique functions. Phasin inhibition reduces the excessive excitability of postsynaptic cells and plays an important role in the generation and regulation of θ and γ oscillations. Alternatively, tonic inhibition could more consistently maintain the amount and duration of postsynaptic depolarization (55).

Postsynaptic inhibition mediated by GABA receptors plays an important role in normal brain function and epilepsy. Blocking GABAergic neurotransmission with drugs can induce acute epileptic discharges and seizures, indicating that disinhibition is a key factor in seizures. In different PTE models and related studies on patients with secondary epilepsy after brain trauma, GABAergic inhibition was weakened, including the loss of inhibitory interneurons, changes in connectivity and anatomical structure, and abnormalities in the postsynaptic GABA receptor (56–58).

TBI is a major cause of death and is typically associated with PTE. TBI causes distinct changes in the neuronal circuits, leading to an imbalance between cortical excitation and inhibition. The change in neurotransmitter concentration was found to be significantly related to the receptor population and cell survival. Subsequent cellular changes may trigger PTE. Changes in the GABA receptor subunit mRNA levels in the thalamic cortex may be related to neuronal degeneration. Although changes in neurotransmitters in PTE have been studied, the specific potential molecular pathways have not been fully elucidated. Astrocyte changes induced by brain injury may impair GABA-mediated neurotransmission, leading to epilepsy. Accordingly, assessing the role of neurotransmitters, especially GABA,

in the changes in acute neurons and astrocytes during TBI may provide a new target for the treatment of PTE (59).

5.4. Calcium

The excessive influx of calcium ions (Ca^{2+}) plays an important role in the occurrence of epilepsy. At the cellular level, epilepsy is caused by the excessive spontaneous discharge of neurons, which is based on cell depolarization caused by transient Ca^{2+} influx. A study performed using the PTE model revealed abnormalities in the Ca^{2+} channel on the presynaptic GABAergic terminals acting on the V-layer vertebral cells in the cortex, which led to a weakening of the inhibitory effect of the nervous system (60). The rapidly increasing levels of extracellular Glu after brain injury play a role in the Ca^{2+} channels. Glu binds to the N-methyl-d-aspartate receptor and activates receptor-operated calcium channels, which can cause Ca^{2+} influx. When Glu binds to KA and QA receptors, it activates Na^{+} channels and depolarizes the cell membrane. When the membrane potential reaches a certain level, the voltage-dependent calcium channel is activated and opened, further intensifying the extracellular Ca^{2+} influx. Excessive Ca^{2+} influx caused by multiple channels eventually leads to the epileptic discharge of neurons (61). After brain injury, the regulatory mechanism of K^{+} is also abnormal, leading to an increase in the extracellular K^{+} concentration, which can promote the transformation of non-explosive neurons into explosive neurons and carry out cluster over discharge, leading to excessive excitation and synchronization of neurons, ultimately causing seizures (62).

5.5. Aquaporin-4

TBI is the most common cause of death and disability among young people. Brain edema is a serious complication of brain trauma, and its occurrence is related to changes in aquaporin (AQP) expression. The most important aquaporin protein in the brain, aquaporin-4 (AQP4), is mainly expressed on astrocyte membranes, and its distribution is extremely uneven. AQP4 is expressed in the endfeet of astrocytes, which are adjacent to blood vessels and the subpial and periventricular regions. This is known as the "polar distribution" of AQP4 and is closely related to water transport. It mainly regulates the bidirectional flow of water in the blood and CSF to maintain ion concentration (63–67). A decrease in AQP-4 can lead to ion regulation dysfunction and epilepsy. Loss of AQP-4 expression is accompanied by a decrease in astrocyte and hippocampal nerve cell regeneration, which can aggravate depressive symptoms (68).

5.6. Oxidative stress

Emerging evidence suggests that acute seizures can cause oxidative stress. On the one hand, due to increased oxygen consumption and reduced antioxidant defenses, neuronal cells are highly susceptible to oxidative damage, and neuronal cells contain large amounts of polyunsaturated fats, which are easily oxidized. On the other hand, the degradation of superoxide dismutase promotes highly reactive peroxynitrite ($ONOO^{-}$), a powerful oxidizing agent that can lead to increased ROS production, the oxidation of DNA, proteins, and lipids, and the loss of ion channel dysfunction, leading to brain damage. Excessive production of free radicals can disrupt intracellular calcium homeostasis, thus affecting neuronal excitability. Therefore, antioxidant therapy may be an important technique for reversing neurodegenerative processes associated with epilepsy (69).

5.7. Other mechanisms

Several studies have redefined the classical role of astrocytes in the brain. Astrocytes were initially considered the main supporting cells (70), functioning as neurons and helping maintain brain homeostasis. Despite early recognition of the role of astrocytes in the injury response (71), their extensive role in the pathogenesis of the inflammatory response continues to be recognized and explored (72). Therefore, astrocytes are not only classified as supporting cells but also as cells that actively and directly participate in many aspects of neural function. Astrocytes are the most abundant cell type in the brain and are involved in the regulation of ion homeostasis, maintenance of the BBB, metabolism of neurotransmitters, and the provision of nutrition and energy support for neuronal function (73). Astrocytes are key components of learning, memory, sleep, and other basic brain functions (5, 23) and play an important role in neuroinflammatory responses.

Astrocytes play a key role in regulating neuronal activity by exchanging neuronal pyruvate for lactic acid to activate neuronal metabolism and increase neuronal NADH levels (7). Astrocytes are also involved in processing neuronal information. Their processing activity involves thousands of synapses and controls neuronal activity through neurotransmitter uptake and release (74). Astrocytes also regulate Glu and GABA availability in the synaptic space, thereby regulating synaptic transmission (25–27). Accordingly, astrocytes may promote PTE via different mechanisms. In the present study, we focused on the mechanisms underlying neuroinflammation. Astrocyte activation is a major cellular component of neuroinflammatory reactions, and glial cell proliferation is common after TBI. Astrocytosis can occur as part of the neuroinflammatory response. In the postmortem TBI human brain, extensive astrocytosis occurs at the main injury site and in the ipsilateral and contralateral brain regions away from the initial injury site (14, 15, 17). Notably, it is impossible to distinguish glial cell proliferation induced by epilepsy from glial cell proliferation alone, which may induce epilepsy in the brains of patients with postmortem epilepsy. Similar glial cell proliferation patterns have been observed in many TBI animal models (3, 7, 10, 18, 19, 40, 75), enabling studies on potential astrocytic mechanisms of epilepsy. The response of astrocytes to TBI involves the death and axonal degeneration of neurons and the rapid release of inflammatory complement system factors, cytokines, and chemokines from microglia, neurons, and astrocytes. Microglia, astrocytes, and neurons are activated and altered following TBI. Activated microglia secrete cytokines such as interleukin-1 α, tumor necrosis factor, and complement component 1 subcomponent q, which can induce the A1 astrocyte phenotype. Astrocytes suffer from gap junction decoupling, synaptic neurotransmitter clearance, and damage to the metabolic cycle. The cytokines interleukin-6, interleukin-1β, transforming growth factor β, and chemokine CCL2 produce a neuroinflammatory environment at high concentrations. Regardless of the source, the release of this cytokine may affect the pathological functions of astrocytes, particularly those involved in physiological signal transduction and epilepsy.

6. Treatment of PTE

Treatment of early post-traumatic seizures does not affect the incidence of post-traumatic seizures. Conventional prophylactic anticonvulsants are not used in patients with head injuries, and treatment in the acute phase does not reduce mortality or disability. A large number of studies have shown that there are different ways to treat PTE, mainly drug therapy and non-drug therapy. Currently, drug therapy is dominant, and non-drug therapies have shown some benefit in the laboratory but have not been established to have any clinical benefit. It has been reported that some drugs such as rapamycin, carbamazepine, phenytoin sodium, sedative-hypnotics, levetiracetam, atorvastatin, losartan, curcumin, and lipoic acid can show antiepileptic effects. In addition, gene therapy, stem cell therapy, and deep brain stimulation have been shown to inhibit the onset and progression of seizures. However, antiepileptic drugs (AEDs) are effective in suppressing epilepsy only if treatment is continued and blood concentrations remain high enough. In addition, long-term treatment with AEDs can produce unwanted side effects, such as chronic cognitive, memory, and behavioral changes, severe hepatotoxicity and neurotoxicity, as well as teratogenic effects and withdrawal effects (76).

7. Discussion

Excitotoxicity, neuroinflammation, oxidative stress, and neurodegeneration are the primary pathological mechanisms underlying PTE. TBI is known to initiate a cycle of neuroinflammatory events that trigger oxidative stress reactions, inducing a cascade of events and cycles that aggravate the acute phase and lead to chronic diseases. This review aimed to understand the mechanisms underlying epilepsy after TBI and to identify, develop, and validate therapeutic strategies to prevent PTE. Accordingly, several key conclusions were drawn: (1) the main sources of cell excitotoxicity after TBI include an increased level of extracellular glutamate, an increase in immune cell infiltration, and crosstalk between glial cells and neurons, which are mainly regulated by the network of cytokines and chemokines; (2) the initial immune response to injury is beneficial, stabilizing the imbalance in the system; (3) overproduction of ROS/RNS leads to mitochondrial damage, which is a continuous process during epilepsy and is related to inflammation and neurodegeneration; (4) proinflammatory cytokines and chemokines are key factors that invade blood cells, microglia, astrocytes, and neurons; (5) long-term excessive production of cytokines, lipids, and chemokines triggers cell death; and (6) leukocyte invasion and activation of microglia leads to late tissue damage.

PTE exhibits phenotypic heterogeneity in humans. Understanding this phenotypic heterogeneity is important for the development of new antiepileptic therapies. Both focal and diffuse mechanisms can cause PTE, and approximately 25–30% of PTE cases are related to medial temporal sclerosis. Although surgery is an alternative therapy, it is not recommended in such cases. Therefore, defibrillators remain the first line of treatment. However, AED is not very effective in the treatment of PTE. Accordingly, it is used to treat symptoms but does not improve the underlying condition. Patients taking antiepileptic drugs (AEDs) typically require long-term treatment. However, some patients experienced serious adverse effects over time. Uncontrolled seizures can lead to increased mortality, a decreased quality of life, comorbidities, and depression. Although many antiepileptic drugs are available, progress has not been made in preventing new seizures. Additionally, the reuse of antiepileptic drugs to prevent seizures has been unsuccessful. Understanding epilepsy as a network disorder requires identifying its early stages before the imbalance spreads to other regions of the brain. However, this identification is not simple because many candidate compounds have multiple functions and target multiple pathways. These approaches may also differ between human and animal models, reducing the translational significance of animal models and emphasizing the importance of appropriate time intervals, dosages, targets, and the design of experiments. Goals must be defined based on different injury mechanisms, and different treatment methods must be adopted at specific time points. Finally, a clear understanding of the molecular mechanisms underlying epilepsy will aid in the development of novel therapeutic targets for PTE.

In this review, we summarize the relevant research on the pathogenesis of PTE. These mechanisms are interrelated and do not exist independently. At present, the relevant mechanisms of PTE have not been clarified, and further research is required. It is the most common form of symptomatic epilepsy. Herein, we describe the inflammatory components of the cellular and molecular mechanisms of the CNS that can promote the development of epilepsy after brain trauma. Although the innate inflammatory response to injury is relatively stable, the comprehensive effect leading to PTE is highly variable and depends on time, location, and individual immune responses. Therefore, diagnostic tools that consider multimodal variables must be developed. Furthermore, the adaptive immune components that play a role in the development of PTE must be recognized. However, these variables require further investigation. As PTE is difficult to treat and is more resistant to first- and second-line antiepileptic treatments, the treatment of specific inflammatory components after TBI is expected to eventually produce meaningful diagnostic tools and effective treatment strategies. Therefore, one of the preconditions for preventing PTE is avoiding TBI as much as possible. Once the relevant mechanisms are revealed, better prevention and treatment strategies for PTE can be developed.

Author contributions

MF, WL, and JT: original draft, design, and methodology. LZ and FL: conceptualization and investigation. JT and ML: supervision and conceptualization. CY and ZX: conceptualization. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that this study was conducted in the absence of commercial or financial relationships that is construed as potential conflicts of interest.

Publisher's note

References

1. Tubi MA, Lutkenhoff E, Blanco MB, McArthur D, Villablanca P, Ellingson B, et al. Early seizures and temporal lobe trauma predict post-traumatic epilepsy: a ongitudinal study. *Neurobiol Dis*. (2019) 123:115–21. doi: 10.1016/j.nbd.2018.05.014

2. Russell WR, Whitty CW. Studies in traumatic epilepsy. I. Factors influencingthe incidence of epilepsy after brain wounds. *J Neurol Neurosurg Psychiatry*. (1952) 15:93–8. doi: 10.1136/jnnp.15.2.93

3. DeGrauw X, Thurman D, Xu L, Kancherla V, DeGrauw T. Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: an analysis of insurance claims data, 2004-2014. *Epilepsy Res*. (2018) 146:41–9. doi: 10.1016/j.eplepsyres.2018.07.012

4. Kossmann T, Hans VH, Imhof HG, Stocker R, Grob P, Trentz O, et al. Intrathecal and serum interleukin-6 and the acute-phase response in patients with severe traumatic brain injuries. *Shock*. (1995) 4:311–7. doi: 10.1097/00024382-199511000-00001

5. Boone DR, Weisz HA, Willey HE, Torres KEO, Falduto MT, Sinha M, et al. Traumatic brain injury induces long-lasting changes in immune and regenerative signaling. *PLoS One*. (2019) 14:e0214741. doi: 10.1371/journal.pone.0214741

6. Hazelton I, Yates A, Dale A, Roodselaar J, Akbar N, Ruitenberg MJ, et al. Exacerbation of acute traumatic brain injury by circulating extracellular vesicles. *J Neurotrauma*. (2018) 35:639–51. doi: 10.1089/neu.2017.5049

7. Mukherjee S, Zeitouni S, Cavarsan CF, Shapiro LA. Increased seizure susceptibility in mice 30 days after fluid percussion injury. *Front Neurol*. (2013) 4:28. doi: 10.3389/fneur.2013.00028

8. Nizamutdinov D, DeMorrow S, McMillin M, Kain J, Mukherjee S, Zeitouni S, et al. Hepatic alterations are accompanied by changes to bile acid transporter-expressing neurons in the hypothalamus after traumatic brain injury. *Sci Rep*. (2017) 7:40112. doi: 10.1038/srep40112

9. Ondruschka B, Schuch S, Pohlers D, Franke H, Dreßler J. Acute phase response after fatal traumatic brain injury. *Int J Legal Med*. (2018) 132:531–9. doi: 10.1007/s00414-017-1768-2

10. Soriano S, Moffet B, Wicker E, Villapol S. Serum amyloid a is expressed in the brain after traumatic brain injury in a sex-dependent manner. *Cell Mol Neurobiol*. (2020) 40:1199–211. doi: 10.1007/s10571-020-00808-3

11. Yang S, Ma Y, Liu Y, Que H, Zhu C, Liu S. Elevated serum haptoglobin after traumatic brain injury is synthesized mainly in liver. *J Neurosci Res*. (2013) 91:230–9. doi: 10.1002/jnr.23159

12. Karve IP, Taylor JM, Crack PJ. The contribution of astrocytes and microglia to traumatic brain injury. *Br J Pharmacol*. (2016) 173:692–702. doi: 10.1111/bph.13125

13. Morganti-Kossmann MC, Satgunaseelan L, Bye N, Kossmann T. Modulation of immune response by head injury. *Injury*. (2007) 38:1392–400. doi: 10.1016/j.injury.2007.10.005

14. Helmy A, Carpenter KL, Menon DK, Pickard JD, Hutchinson PJ. The cytokine response to human traumatic brain injury: temporal profiles and evidence for cerebral parenchymal production. *J Cereb Blood Flow Metab*. (2011) 31:658–70. doi: 10.1038/jcbfm.2010.142

15. Kumar RG, Diamond ML, Boles JA, Berger RP, Tisherman SA, Kochanek PM, et al. Acute CSF interleukin-6 trajectories after TBI: associations with neuroinflammation, polytrauma, and outcome. *Brain Behav Immun*. (2015) 45:253–62. doi: 10.1016/j.bbi.2014.12.021

16. Witcher KG, Bray CE, Dziabis JE, McKim DB, Benner BN, Rowe RK, et al. Traumatic brain injury-induced neuronal damage in the somatosensory cortex causes formation of rod-shaped microglia that promote astrogliosis and persistent neuroinflammation. *Glia*. (2018) 66:2719–36. doi: 10.1002/glia.23523

17. Wofford KL, Harris JP, Browne KD, Brown DP, Grovola MR, Mietus CJ, et al. Rapid neuroinflammatory response localized to injured neurons after diffuse traumatic brain injury in swine. *Exp Neurol*. (2017) 290:85–94. doi: 10.1016/j.expneurol.2017.01.004

18. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med*. (1998) 338:20–4. doi: 10.1056/NEJM199801013380104

19. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia*. (1993) 34:453–8. doi: 10.1111/j.1528-157.1993.tb02586.x

20. Caveness WF. Epilepsy, a product of trauma in our time. *Epilepsia*. (1976) 17:207–15. doi: 10.1111/j.1528-1157.1976.tb03398.x

21. Caveness WF, Walker AE, Ascroft PB. Incidence of posttraumatic epilepsy in Korean veterans as compared with those from world war I and world war II. *J Neurosurg*. (1962) 19:122–9. doi: 10.3171/jns.1962.19.2.0122

22. Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: an overview. *Clin Neurol Neurosurg*. (2006) 108:433–9. doi: 10.1016/j.clineuro.2005.09.001

23. Beghi E. Overview of studies to prevent posttraumatic epilepsy. *Epilepsia*. (2003) 44:21–6. doi: 10.1046/j.1528-1157.44.s10.1.x

24. Teasell R, Bayona N, Lippert C, Villamere J, Hellings C. Post-traumatic seizure disorder following acquired brain injury. *Brain Inj*. (2007) 21:201–14. doi: 10.1080/02699050701201854

25. Wang F, Wang X, Shapiro LA, Cotrina ML, Liu W, Wang EW, et al. NKCC1 up-regulation contributes to early post-traumatic seizures and increased post-traumatic seizure susceptibility. *Brain Struct Funct*. (2017) 222:1543–56. doi: 10.1007/s00429-016-1292-z

26. Irimia A, Van Horn JD. Epileptogenic focus localization in treatment-resistant post-traumatic epilepsy. *J Clin Neurosci*. (2015) 22:627–31. doi: 10.1016/j.jocn.2014.09.019. Epub 2014 Oct 31

27. Mootz W, Schöndorf J, Hübers H. Fluoreszenzmikroskopischer Histaminnachweis in den Mastzellen der menschlichen Gaumenmandel: fluorescence microscopy demonstration of histamine in the mast cells of the human tonsil. *Z Laryngol Rhinol Otol*. (1971) 50:140–5.

28. Kettenmann H, Verkhratsky A. Neuroglia: the 150 years after. *Trends Neurosci*. (2008) 31:653–9. doi: 10.1016/j.tins.2008.09.003

29. Pitkänen, A, Paananen, T, Kyyriäinen, J, Das Gupta, S, Heiskanen, M, Vuokila, N, et al Biomarkers for posttraumaticepilepsy. *Epilepsy Behav*. (2021) 121:107080. doi: 10.1016/j.yebeh.2020.107080. Epub 2020 Apr 18.

30. Aungst S, England PM, Thompson SM. Critical role of trkB receptors in reactive axonal sprouting and hyperexcitability after axonal injury. *J Neurophysiol*. (2013) 109:813–24. doi: 10.1152/jn.00869.2012

31. Gill R, Chang PK, Prenosil GA, Deane EC, McKinney RA. Blocking brain-derived neurotrophic factor inhibits injury-induced hyperexcitability of hippocampal CA3neurons. *Eur J Neurosci*. (2013) 38:3554–66. doi: 10.1111/ejn.12367

32. King CE, Canty AJ, Vickers JC. Alterations in neurofilaments associated with reactive brain changes and axonal sprouting following acute physical injury to the rat neocortex. *Neuropathol Appl Neurobiol*. (2001) 27:115–26. doi: 10.1046/j.1365-2990.2001.00317.x

33. Jin X, Prince DA, Huguenard JR. Enhanced excitatory synaptic connectivity in layer v pyramidal neurons of chronically injured epileptogenic neocortex in rats. *J Neurosci*. (2006) 26:4891–900. doi: 10.1523/JNEUROSCI.4361-05.2006

34. Bao YH, Bramlett HM, Atkins CM, Truettner JS, Lotocki G, Alonso OF, et al. Post-traumatic seizures exacerbate histopathological damage after fluid-percussion brain injury. *J Neurotrauma*. (2011) 28:35–42. doi: 10.1089/neu.2010.1383

35. Shultz SR, Cardamone L, Liu YR, Hogan RE, Maccotta L, Wright DK, et al. Can structural or functional changes following traumatic brain injury in the rat predict epileptic outcome? *Epilepsia*. (2013) 54:1240–50. doi: 10.1111/epi.12223

36. Hunt RF, Boychuk JA, Smith BN. Neural circuit mechanisms of post-traumatic epilepsy. *Front Cell Neurosci*. (2013) 7:89. doi: 10.3389/fncel.2013.00089

37. Hu L, Yang S, Jin B, Wang C. Advanced neuroimaging role in traumatic brain injury: a narrative review. *Front Neurosci*. (2022) 16:872609. doi: 10.3389/fnins.2022.872609

38. Sharma, S, Tiarks, G, Haight, J, and Bassuk, AG. Neuropathophysiological mechanisms and treatment strategies for post-traumatic epilepsy. *Front Mol Neurosci*. (2021) 14:612073. doi: 10.3389/fnmol.2021.612073

39. Tomkins O, Feintuch A, Benifla M, Cohen A, Friedman A, Shelef I. Blood-brain barrier breakdown following traumatic brain injury: a possible role in posttraumatic epilepsy. *Cardiovasc Psychiatry Neurol*. (2011) 2011:765923. doi: 10.1155/2011/765923

40. Dadas A, Janigro D. Breakdown of blood brain barrier as a mechanism of post-traumatic epilepsy. *Neurobiol Dis*. (2019) 123:20–6. doi: 10.1016/j.nbd.2018.06.022

41. Tchekalarova J, Atanasova D, Kortenska L, Atanasova M, Lazarov N. Chronic agomelatine treatment prevents comorbid depression in the post-status epilepticus model of acquired epilepsy through suppression of inflammatory signaling. *Neurobiol Dis*. (2018) 115:127–44. doi: 10.1016/j.nbd.2018.04.005

42. Zhao H, Lin Y, Chen S, Li X, Huo H. 5-HT3 receptors: a potential therapeutic target for epilepsy. *Curr Neuropharmacol*. (2018) 16:29–36. doi: 10.2174/1570159X15666170508170412

43. Darrah SD, Miller MA, Ren D, Hoh NZ, Scanlon JM, Conley YP, et al. Genetic variability in glutamic acid decarboxylase genes: associations with post-traumatic seizures after severe TBI. *Epilepsy Res*. (2013) 103:180–94. doi: 10.1016/j.eplepsyres.2012.07.006

44. Goodrich GS, Kabakov AY, Hameed MQ, Dhamne SC, Rosenberg PA, Rotenberg A. Ceftriaxone treatment after traumatic brain injury restores expression of the glutamate transporter, GLT-1, reduces regional gliosis, and reduces post-traumatic seizures in the rat. *J Neurotrauma*. (2013) 30:1434–41. doi: 10.1089/neu.2012.2712

45. Kharlamov EA, Lepsveridze E, Meparishvili M, Solomonia RO, Lu B, Miller ER, et al. Alterations of GABA(a) and glutamate receptor subunits and heat shock protein in rat hippocampus following traumatic brain injury and in posttraumatic epilepsy. *Epilepsy Res*. (2011) 95:20–34. doi: 10.1016/j.eplepsyres.2011.02.008

46. Eid T, Hammer J, Rundén-Pran E, Roberg B, Thomas MJ, Osen K, et al. Increased expression of phosphate-activated glutaminase in hippocampal neurons in human mesial temporal lobe epilepsy. *Acta Neuropathol*. (2007) 113:137–52. doi: 10.1007/s00401-006-0158-5

47. Kugaya A, Sanacora G. Beyond monoamines: glutamatergic function in mood disorders. *CNS Spectr*. (2005) 10:808–19. doi: 10.1017/s1092852900010403

48. Baran H, Gramer M, Hönack D, Löscher W. Systemic administration of kainate induces marked increases of endogenous kynurenic acid in various brain regions and plasma of rats. *Eur J Pharmacol*. (1995) 286:167–75. doi: 10.1016/0014-2999(95)00443-o

49. Ben-Ari Y, Cossart R. Kainate, a double agent that generates seizures: two decades of progress. *Trends Neurosci*. (2000) 23:580–7. doi: 10.1016/s0166-2236(00)01659-3

50. Westbrook GL, Lothman EW. Cellular and synaptic basis of kainic acid-induced hippocampal epileptiform activity. *Brain Res*. (1983) 273:97–109. doi: 10.1016/0006-8993(83)91098-3

51. DeFelipe J, Huntley GW, del Río MR, Sola RG, Morrison JH. Microzonal decreases in the immunostaining for non-NMDA ionotropic excitatory amino acid receptor subunits GluR 2/3 and GluR 5/6/7 in the human epileptogenic neocortex. *Brain Res*. (1994) 657:150–8. doi: 10.1016/0006-8993(94)90962-8

52. Abel, JJ, Rowntree, LG, and Turner, BB. Plasma removal with return of corpuscles (plasmaphaeresis). *The Journal of Pharmacology and experimental therapeutics Transfus Sci* (1990) 11:166–77.

53. Walls AB, Waagepetersen HS, Bak LK, Schousboe A, Sonnewald U. The glutamine-glutamate/GABA cycle: function, regional differences in glutamate and GABA production and effects of interference with GABA metabolism. *Neurochem Res*. (2015) 40:402–9. doi: 10.1007/s11064-014-1473-1

54. Olsen RW, Sieghart W. GABA a receptors: subtypes provide diversity of function and pharmacology. *Neuropharmacology*. (2009) 56:141–8. doi: 10.1016/j.neuropharm.2008.07.045

55. Farrant M, Nusser Z. Variations on an inhibitory theme: phasic and tonic activation of GABA(a) receptors. *Nat Rev Neurosci*. (2005) 6:215–29. doi: 10.1038/nrn1625

56. André V, Marescaux C, Nehlig A, Fritschy JM. Alterations of hippocampal GAbaergic system contribute to development of spontaneous recurrent seizures in the rat lithium-pilocarpine model of temporal lobe epilepsy. *Hippocampus*. (2001) 11:452–68. doi: 10.1002/hipo.1060

57. Faria LC, Prince DA. Presynaptic inhibitory terminals are functionally abnormal in a rat model of posttraumatic epilepsy. *J Neurophysiol*. (2010) 104:280–90. doi: 10.1152/jn.00351.2010

58. Jin X, Huguenard JR, Prince DA. Reorganization of inhibitory synaptic circuits in rodent chronically injured epileptogenic neocortex. *Cereb Cortex*. (2011) 21:1094–104. doi: 10.1093/cercor/bhq181

59. Akyuz E, Polat AK, Eroglu E, Kullu I, Angelopoulou E, Paudel YN. Revisiting the role of neurotransmitters in epilepsy: an updated review. *Life Sci*. (2021) 265:118826. doi: 10.1016/j.lfs.2020.118826

60. Faria LC, Parada I, Prince DA. Interneuronal calcium channel abnormalities in posttraumatic epileptogenic neocortex. *Neurobiol Dis*. (2012) 45:821–8. doi: 10.1016/j.nbd.2011.11.006

61. Gurkoff GG, Shahlaie K, Lyeth BG. In vitro mechanical strain trauma alters neuronal calcium responses: Implications for posttraumatic epilepsy. *Epilepsia*. (2012) 53:53–60. doi: 10.1111/j.1528-1167.2012.03475.x

62. Stewart TH, Eastman CL, Groblewski PA, Fender JS, Verley DR, Cook DG, et al. Chronic dysfunction of astrocytic inwardly rectifying K+ channels specific to the neocortical epileptic focus after fluid percussion injury in the rat. *J Neurophysiol*. (2010) 104:3345–60. doi: 10.1152/jn.00398.2010

63. Amiry-Moghaddam M, Ottersen OP. The molecular basis of water transport in the brain. *Nat Rev Neurosci*. (2003) 4:991–1001. doi: 10.1038/nrn1252

64. Badaut J, Ashwal S, Adami A, Tone B, Recker R, Spagnoli D, et al. Brain water mobility decreases after astrocytic aquaporin-4 inhibition using RNA interference. *J Cereb Blood Flow Metab*. (2011) 31:819–31. doi: 10.1038/jcbfm.2010.163

65. Habib P, Dang J, Slowik A, Victor M, Beyer C. Hypoxia-induced gene expression of aquaporin-4, cyclooxygenase-2 and hypoxia-inducible factor 1α in rat cortical astroglia is inhibited by 17β-estradiol and progesterone. *Neuroendocrinology*. (2014) 99:156–67. doi: 10.1159/000362279

66. Liu H, Qiu G, Zhuo F, Yu W, Sun S, Li F, et al. Lost polarization of Aquaporin4 and Dystroglycan in the Core lesion after traumatic brain injury suggests functional divergence in evolution. *Biomed Res Int*. (2015) 2015:471631:1–10. doi: 10.1155/2015/471631

67. Lopez-Rodriguez AB, Acaz-Fonseca E, Viveros MP, Garcia-Segura LM. Changes in cannabinoid receptors, aquaporin 4 and vimentin expression after traumatic brain injury in adolescent male mice. Association with edema and neurological deficit. *PLoS One*. (2015) 10:e0128782. doi: 10.1371/journal.pone.0128782

68. Conway CR, Udaiyar A, Schachter SC. Neurostimulation for depression in epilepsy. *Epilepsy Behav*. (2018) 88:25–32. doi: 10.1016/j.yebeh.2018.06.007

69. Mohamed AM, Ali DA, Kolieb E, Abdelaziz EZ. Ceftriaxone and selenium mitigate seizures and neuronal injury in pentylenetetrazole-kindled rats: oxidative stress and inflammatory pathway. *Int Immunopharmacol*. (2023) 120:110304. doi: 10.1016/j.intimp.2023.110304

70. Verkhratsky A, Ho MS, Vardjan N, Zorec R, Parpura V. General pathophysiology of Astroglia. *Adv Exp Med Biol*. (2019) 1175:149–79. doi: 10.1007/978-981-13-9913-8_7

71. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized,double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med*. (1990) 323:497–502. doi: 10.1056/NEJM199008233230801

72. Oberheim NA, Takano T, Han X, He W, Lin JH, Wang F, et al. Uniquely hominid features of adult human astrocytes. *J Neurosci*. (2009) 29:3276–87. doi: 10.1523/JNEUROSCI.4707-08.2009

73. Halassa MM, Haydon PG. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. *Annu Rev Physiol*. (2010) 72:335–55. doi: 10.1146/annurev-physiol-021909-135843

74. Weber B, Barros LF. The astrocyte: powerhouse and recycling center. *Cold Spring Harb Perspect Biol*. (2015) 7:a020396. doi: 10.1101/cshperspect.a020396

75. Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam head injury study. *Neurology*. (1985) 35:1406–14. doi: 10.1212/wnl.35.10.1406

76. Lu W, Wu Z, Zhang C, Gao T, Ling X, Xu M, et al. Jujuboside a exhibits an Antiepileptogenic effect in the rat model via protection against traumatic epilepsy-induced oxidative stress and inflammatory responses. *Evid Based Complement Alternat Med*. (2022) 2022:7792791–9. doi: 10.1155/2022/7792791

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The prognostic value of an age-adjusted BIG score in adult patients with traumatic brain injury

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Background: The base deficit, international normalized ratio, and Glasgow Coma Scale (BIG) score was previously developed to predict the outcomes of pediatric trauma patients. We designed this study to explore and improve the prognostic value of the BIG score in adult patients with traumatic brain injury (TBI).

Methods: Adult patients diagnosed with TBI in a public critical care database were included in this observational study. The BIG score was calculated based on the Glasgow Coma Scale (GCS), the international normalized ratio (INR), and the base deficit. Logistic regression analysis was performed to confirm the association between the BIG score and the outcome of included patients. Receiver operating characteristic (ROC) curves were drawn to evaluate the prognostic value of the BIG score and novel constructed models.

Results: In total, 1,034 TBI patients were included in this study with a mortality of 22.8%. Non-survivors had higher BIG scores than survivors ($p < 0.001$). The results of multivariable logistic regression analysis showed that age ($p < 0.001$), pulse oxygen saturation (SpO_2) ($p = 0.032$), glucose ($p = 0.015$), hemoglobin ($p = 0.047$), BIG score ($p < 0.001$), subarachnoid hemorrhage ($p = 0.013$), and intracerebral hematoma ($p = 0.001$) were associated with in-hospital mortality of included patients. The AUC (area under the ROC curves) of the BIG score was 0.669, which was not as high as in previous pediatric trauma cohorts. However, combining the BIG score with age increased the AUC to 0.764. The prognostic model composed of significant factors including BIG had the highest AUC of 0.786.

Conclusion: The age-adjusted BIG score is superior to the original BIG score in predicting mortality of adult TBI patients. The prognostic model incorporating the BIG score is beneficial for clinicians, aiding them in making early triage and treatment decisions in adult TBI patients.

KEYWORDS

BIG score, traumatic brain injury, prognosis, trauma score, adult

Introduction

As the leading cause of mortality and disability in trauma patients, traumatic brain injury (TBI) brings damage to victims and their families' quality of life and economic burden to society. A recent study estimated that nearly 69 million individuals are diagnosed with TBI annually in the world (1). The high mortality of TBI patients makes early triage and

clinical intervention extremely important. Many trauma scores have been developed to assess the injury severity of TBI and to predict the outcome of trauma patients, such as the revised trauma score (RTS), the injury severity score (ISS), and the comprehensive trauma revised injury severity score (TRISS) (2–5). Specific scoring systems aimed at predicting the outcome of TBI patients were also developed and validated, including the CRASH model and IMPACT model (6, 7). However, these scores composed of radiologic characteristics and other anatomical factors are too complex and time-consuming for clinicians making patient triage and treatment decisions in the early stage after initial brain injury.

The BIG (composed of base deficit, international normalized ratio, and Glasgow Coma Scale) score is a pediatric trauma score that was initially developed to assess children facing military and civilian traumatic injuries (8). It has been proven to accurately predict the mortality rate of pediatric trauma patients admitted to military trauma systems. Several subsequent studies externally confirmed the good performance of the BIG score in predicting the mortality of similar pediatric trauma patients (9–11). Moreover, one study confirmed that the BIG score in admission was associated with functional outcomes at hospital discharge in pediatric TBI patients (12). The BIG score performed better than other pediatric trauma scoring systems and was validated with similar accuracy in a separate pediatric population (8). A BIG score of <12 points suggests a mortality of <5%, whereas a cutoff of >26 points corresponds to a mortality of >50% (13). In addition, researchers also explored the prognostic value of the BIG score in non-specific adult trauma patients and found that the BIG score had a comparable predictive performance with TRISS and the probability of survival (PS09) score (14). Given that aging is a factor that affects the prognosis of trauma patients, we proposed to establish an age-adjusted BIG score to better predict the mortality of patients with trauma.

It was mentioned in all the above studies that the superiority of the BIG score was its availability and simplicity. Based on these findings, we designed this study to explore the prognostic value of the BIG score and compared it with other trauma triage scores in homogeneous adult TBI patients.

Materials and methods

Data source

This observational study was performed using data from the Multiparameter Intelligent Monitoring in Intensive Care Database III (MIMIC-III database), which was a large critical care database including patients admitted to ICUs (intensive care unit) of the Beth Israel Deaconess Medical Center between 2001 and 2012. This freely available database was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology (MIT). All data of participants in this public database were deidentified and anonymized. We obtained access to utilize data from the MIMIC III database after passing the National Institutes of Health (NIH) web-based training course and the Protecting Human Research Participants examination. All needed data, including age, sex, vital signs, laboratory tests, diagnoses, length of hospital stay, records of operation, and blood transfusion of this study were extracted by us using Navicat Premium 12 (PremiumSoft, Hong Kong). The BIG score was calculated by base deficit + 2.5 × INR + (15-GCS). The computing methods of other trauma scoring systems, including RTS, new trauma score (NTS), and GCS, age, and systolic arterial pressure score (GAP), were referred to in previous studies (15, 16). The primary outcome of this study was in-hospital mortality.

Participants

Patients with head injuries from the MIMIC-III database were enrolled for this study based on ICD-9 codes (800.00–801.99; 803.00–804.99; 850.0–854.19). However, patients were excluded from this study if they met any one of the following criteria: (1) diagnosed only with extracranial injury including scalp injury and skull fracture and head AIS < 3; (2) age < 18 years; (3) incomplete records of GCS, INR, and base deficit; (4) discharged within 24 h following admission (due to the hasty process, these patients did not receive standard medical treatment and examination, so they lacked many related variables). After exclusion, a total of 1,034 patients were included in the final cohort. The complete flowchart of participant inclusion is shown in Figure 1.

Statistical analysis

We utilized Kolmogorov–Smirnov tests to verify the normality of included variables. All continuous variables included in this study were expressed as median (interquartile range) and differences between groups of continuous variables were testified by the Mann–Whitney *U*-test because of their non-normal distribution. Categorical variables were expressed as numbers (percentage) and differences between groups of categorical variables were analyzed by the chi-square test. Univariable logistic regression was performed first and then, stepwise multivariable logistic regression with the entry method including significant variables in the univariable logistic regression was sequentially performed to explore the independent relationship between BIG score, other risk factors, and in-hospital mortality of included patients. The odds ratio (OR) and 95% confidence intervals (CI) of each factor were also shown. Then, multivariable logistic regression analysis was also performed to construct an age-adjusted BIG score and the multi-factor prognostic model. The nomogram of this multi-factor prognostic model was drawn for convenient clinical use. A calibration plot was drawn to evaluate the fit of the multi-factor prognostic model. Receiver operating characteristic (ROC) curves were drawn to evaluate the discriminatory ability to predict outcomes of included patients. The Youden index was used to identify cutoff values. We used the *Z*-test to compare the predictive values between factors and models.

A P-value < 0.05 was considered to be statistically significant. We used SPSS 22.0 Windows software (SPSS, Inc, Chicago, IL) and

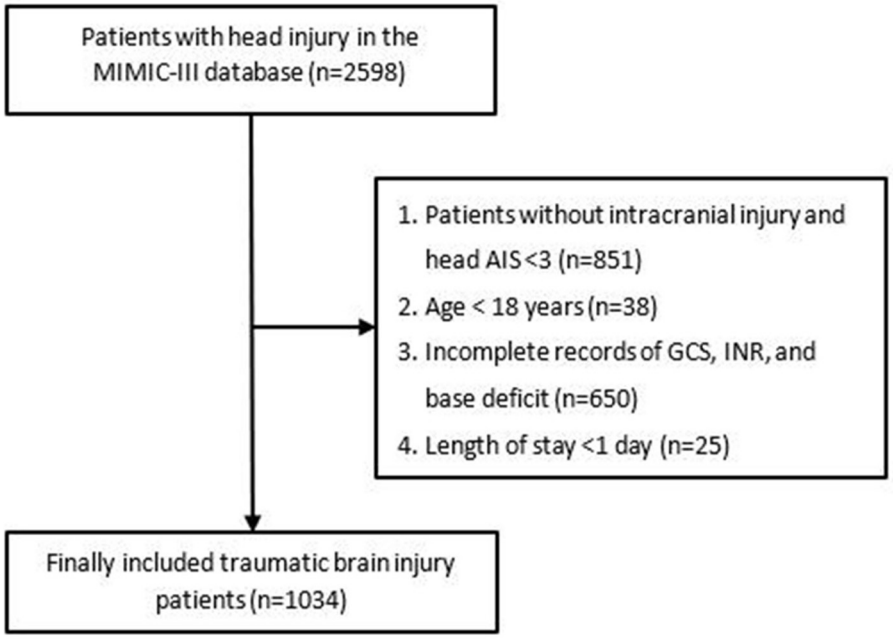

FIGURE 1
Flowchart of patients' inclusion.

R (version 3.6.1; R Foundation) for all statistical analyses and for drawing the figures.

Results

Baseline comparison of included TBI patients based on in-hospital outcomes

A total of 1,034 patients were included in this study with 798 survivors and 236 non-survivors (Table 1). The mortality rate and male ratio of included patients were 22.8 and 59.7%, respectively. The incidence of diabetes mellitus ($p = 0.015$) and hypertension ($p = 0.004$) were both higher among non-survivors. Vital signs including systolic blood pressure, diastolic blood pressure, and respiratory rate were not different between survivors and non-survivors. However, non-survivors had significantly lower heart rate ($p = 0.032$). Pulse oxygen saturation (SpO_2) did not differ between those two groups, whereas the GCS score of non-survivors was lower than that of survivors with statistical significance ($p < 0.001$). Results of laboratory tests showed that non-survivors had a higher level of blood glucose ($p < 0.001$), base deficit ($p = 0.047$), and INR ($p < 0.001$), while the level of hemoglobin ($p < 0.001$) and platelet ($p < 0.001$) were significantly lower in non-survivors. Furthermore, the BIG score of non-survivors was significantly higher than that of survivors ($p < 0.001$), whereas survivors had a higher score of RTS ($p < 0.001$), NTS ($p < 0.001$), and GAP ($p < 0.001$). Results of injury types presented that non-survivors were more frequently diagnosed with subarachnoid hemorrhage ($p = 0.005$) and intracerebral hematoma ($p = 0.012$).

Univariate and multivariable logistic regression analysis of risk factors for in-hospital mortality of included TBI patients

Results of univariate logistic regression analysis indicated that age ($p < 0.001$), diabetes mellitus ($p = 0.016$), hypertension ($p = 0.004$), glucose ($p < 0.001$), BIG score ($p < 0.001$), occurrence of subarachnoid hemorrhage ($p = 0.005$), and intracerebral hematoma ($p = 0.010$) were positively associated with poor outcomes of included patients (Table 2), whereas heart rate ($p = 0.026$), SpO_2 ($p = 0.015$), hemoglobin ($p < 0.001$), and platelet ($p = 0.046$) were inversely related with poor in-hospital outcomes. All variables were then included in multivariable analysis. After adjusting confounded factors, age ($p < 0.001$), SpO_2 ($p = 0.032$), glucose ($p = 0.015$), hemoglobin ($p = 0.047$), BIG score ($p < 0.001$), subarachnoid hemorrhage ($p = 0.013$), and intracerebral hematoma ($p = 0.001$) were still correlated with in-hospital mortality of included TBI patients.

Construction of the age-adjusted BIG score and multi-factor prognostic model

Multivariable logistic regression was utilized to construct an age-adjusted BIG score. Utilizing regression coefficients of age and BIG score, we calculated the age-adjusted BIG score by $0.38 \times \text{age} + \text{BIG score}$ for convenient application. Then, a multi-factor prognostic model was also constructed by multivariable logistic regression using the abovementioned seven

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TABLE 1 Baseline comparison of TBI patients divided by the survival status.

Variables	Total patients ($N = 1,034$)	Survivors (798, 77.2%)	Non-survivors (236, 22.8%)	*p*
Age (years)	67 (46–81)	63 (42–80)	77 (62–86)	<0.001
Male gender (%)	617 (59.7%)	489 (61.3%)	128 (54.2%)	0.053
Comorbidities				
Diabetes mellitus (%)	82 (17.6%)	128 (16.0%)	54 (22.9%)	0.015
Hypertension (%)	399 (38.6%)	289 (36.2%)	110 (46.6%)	0.004
Hyperlipidemia (%)	126 (12.2%)	95 (11.9%)	31 (13.1%)	0.612
Cerebral vascular disease (%)	17 (1.6%)	12 (1.5%)	5 (2.1%)	0.514
Coronary heart disease (%)	148 (14.3%)	109 (13.7%)	39 (16.5%)	0.269
Vital sings in admission				
Systolic blood pressure (mmHg)	128 (118–147)	128 (118–146)	128 (119–149)	0.565
Diastolic blood pressure (mmHg)	64 (56–75)	64 (57–75)	64 (51–74)	0.169
Heart rate (min^{-1})	84 (72–99)	85 (73–99)	82 (71–95)	0.032
Respiratory rate (min^{-1})	18 (15–21)	18 (15–21)	18 (15–21)	0.751
SpO_2 (%)	99 (97–100)	99 (97–100)	99 (97–100)	0.347
GCS in admission	8 (6–14)	10 (6–14)	6 (3–9)	<0.001
Laboratory tests				
Glucose (mg/dL)	139 (114–174)	134 (112–165)	159 (131–193)	<0.001
Hemoglobin (g/dL)	12.5 (11.1–13.8)	12.7 (11.4–14.0)	12 (10.3–13.1)	<0.001
Platelet ($\times 10^9$/L)	224 (176–282)	227 (183–284)	211 (156–260)	<0.001
pH	7.38 (7.32–7.44)	7.38 (7.32–7.44)	7.38 (7.31–7.45)	0.958
Base deficit (mmol/L)	0 (−2 to 3)	0 (−2 to 3)	0 (−2 to 4)	0.047
INR	1.1 (1.1–1.3)	1.1 (1.1–1.3)	1.2 (1.1–1.7)	<0.001
BIG score	10 (5–15)	9 (4–14)	13 (9–18)	<0.001
RTS score	10 (10–11)	10 (10–12)	10 (8–10)	<0.001
NTS score	15 (13–19)	15 (14–20)	14 (11–15)	<0.001
GAP score	15 (12–19)	15 (13–19)	12 (10–15)	<0.001
Surgical intervention (%)	310 (30.0%)	231 (28.9%)	79 33.5%)	0.182
Blood transfusion (%)	457 (44.2%)	343 (43.0%)	114 (48.3%)	0.148
Injury classification				
Epidural hematoma (%)	20 (1.9%)	17 (2.1%)	3 (1.3%)	0.591
Subdural hematoma (%)	444 (42.9%)	333 (41.7%)	111 (32.6%)	0.149
Subarachnoid hemorrhage (%)	264 (25.5%)	187 (23.4%)	77 (32.6%)	0.005
Intracerebral hematoma (%)	144 (13.9%)	99 (12.4%)	45 (19.1%)	0.012
Length of ICU stay (days)	3 (2–7)	3 (2–7)	4 (2–7)	0.587
Length of hospital stay (days)	9 (5–15)	10 (6–17)	5 (2–10)	<0.001

SpO_2, pulse oxygen saturation; GCS, Glasgow Coma Scale; INR, International Normalized Ratio; RTS, Revised New Trauma Score; NTS, New Trauma Score; GAP, The GCS; Age and Systolic Arterial Pressure score.

TABLE 2 Univariate and multivariable analysis of risk factors for in-hospital mortality in included TBI patients.

Variables	Unadjusted analysis			Adjusted analysis		
	OR	95%CI	*p*	OR	95%CI	*p*
Age	1.029	1.021–1.038	<0.001	1.039	1.028–1.050	<0.001
Male gender	0.749	0.559–1.004	0.053			
Diabetes mellitus	1.553	1.086–2.221	0.016	0.991	0.643–1.511	0.969
Hypertension	1.538	1.146–2.062	0.004	1.186	0.832–1.692	0.344
Hyperlipidemia	1.119	0.725–1.728	0.612			
Cerebral vascular disease	1.418	0.494–4.066	0.516			
Coronary heart disease	1.251	0.840–1.864	0.270			
Systolic blood pressure	1.000	0.996–1.004	0.924			
Diastolic blood pressure	0.997	0.990–1.004	0.347			
Heart rate	0.992	0.985–0.999	0.026	0.995	0.986–1.003	0.207
Respiratory rate	0.997	0.968–1.026	0.825			
SpO_2	0.953	0.917–0.991	0.015	0.956	0.912–0.992	0.032
Glucose	1.006	1.004–1.009	<0.001	1.003	1.001–1.006	0.015
Hemoglobin	0.836	0.781–0.894	<0.001	0.921	0.849–0.999	0.047
Platelet	0.998	0.997–1.000	0.046	1.000	0.998–1.002	0.964
pH	1.095	0.479–2.500	0.830			
BIG score	1.081	1.059–1.104	<0.001	1.111	1.084–1.14	<0.001
Surgical intervention	1.235	0.905–1.685	0.183			
Blood transfusion	1.240	0.926–1.659	0.148			
Epidural hematoma	0.592	0.172–2.036	0.405			
Subdural hematoma	1.240	0.926–1.660	0.148			
Subarachnoid hemorrhage	1.582	1.152–2.174	0.005	1.577	1.097–2.259	0.013
Intracerebral hematoma	1.663	1.130–2.450	0.010	2.121	1.358–3.289	0.001

SpO_2, pulse oxygen saturation; OR, odds ratio; CI, confidence interval.

significant factors, which were age, SpO_2, glucose, hemoglobin, BIG score, subarachnoid hemorrhage, and intracerebral hematoma. The nomogram of this multi-factor prognostic model was drawn to evaluate its accuracy (Figure 2A). The calibration plot showed good consistency between the actual probability and predicted probability of in-hospital mortality (Figure 2B).

Comparison of prognostic values between BIG score, age-adjusted BIG score, and the constructed prognostic model

As shown in Table 3, the AUC value of single GCS and BIG scores were 0.699 and 0.669, respectively (Figure 3). The age-adjusted BIG score had higher AUC (AUC = 0.764) than GCS ($Z = 15.795$, $p < 0.001$) and BIG ($Z = 5.352$, $p < 0.001$). The constructed prognostic model composed of seven factors (age, SpO_2, glucose, hemoglobin, BIG, subarachnoid hemorrhage, and intracerebral hematoma) had the highest AUC (AUC = 0.786).

Discussion

In our study, the BIG score was not a valuable risk stratification tool for adult TBI patients. However, the age-adjusted BIG score performed well in predicting outcomes with an AUC of 0.764. The prognostic value of the age-adjusted BIG score was superior to the readily available physiological scoring system RTS. Combining four indicators of mortality (age, base deficit, international normalized ratio, and Glasgow Coma Scale) in trauma patients, the age-adjusted BIG score could comprehensively reflect the injury severity and possible progression of adult traumatic patients.

As an indicator of shock, base deficit was confirmed to be associated with injury severity and mortality in pediatric and adult trauma patients (17–20). Researchers also concluded that base deficit was a useful predictor of coagulation decompensation and shock-related complications after trauma (21, 22). One study found

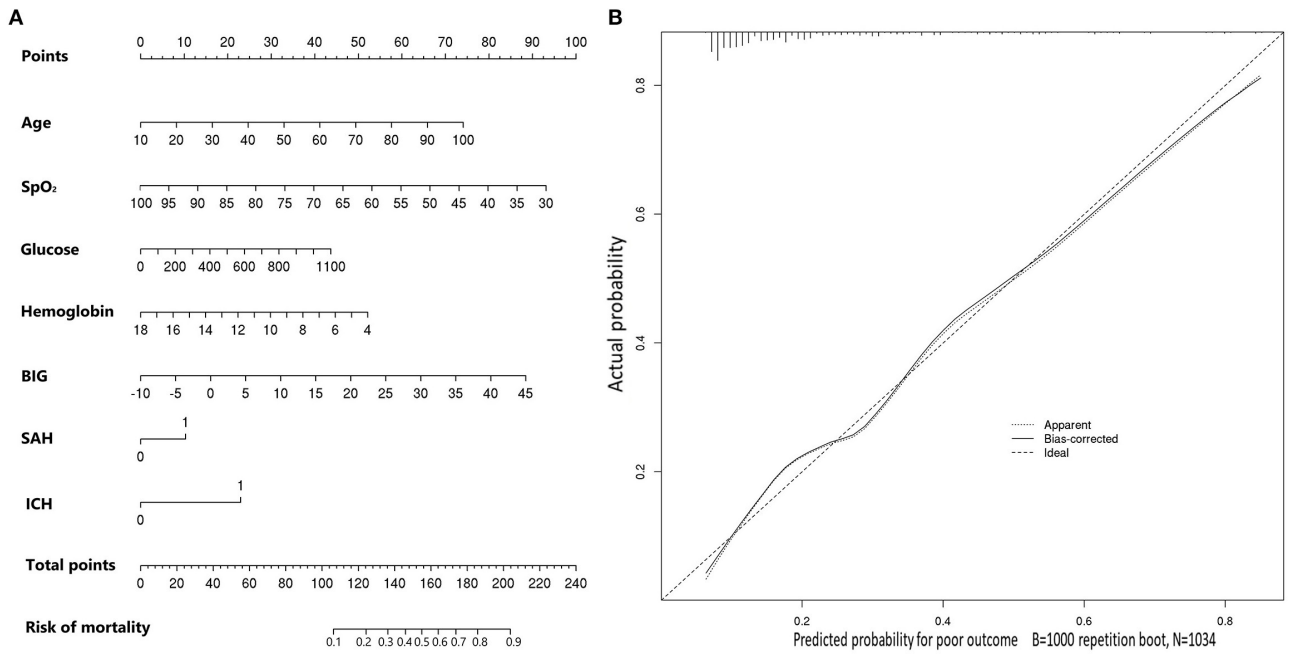

FIGURE 2
(A) Nomogram of the constructed prognostic model for predicting in-hospital mortality in included TBI patients. **(B)** Calibration plot of the constructed prognostic model for predicting in-hospital mortality in included TBI patients.

TABLE 3 AUC value of age adjusted BIG, other trauma triage score and constructed prognostic model.

	AUC	95% CI	Sensitivity	Specificity	Youden index	Best cutoff
NTS	0.664	0.625–0.703	0.692	0.555	0.247	15
GAP	0.703	0.666–0.740	0.732	0.585	0.317	14
RTS	0.639	0.600–0.678	0.425	0.792	0.217	11
GCS	0.699	0.661–0.737	0.739	0.627	0.366	7
BIG	0.669	0.629–0.708	0.614	0.635	0.250	12
Age adjusted BIG	0.764	0.730–0.797	0.784	0.619	0.403	0.20
Prognostic model	0.786	0.754–0.818	0.703	0.722	0.425	0.24

AUC, area under the receiver operating characteristic curve; CI, confidence interval; NTS, New Trauma Score; GAP, The GCS, Age and Systolic Arterial Pressure score; RTS, Revised Trauma Score; GCS, Glasgow Coma Scale.
The prognostic model is composed of age, SpO_2, glucose, hemoglobin, BIG, subarachnoid hemorrhage and intracerebral hematoma.

that an increased base deficit was associated with prolonged partial thromboplastin and prothrombin times and low protein C levels in trauma patients (23). A Evaluating level of base deficit could help physicians decide the requirements of early transfusion to avoid the development of hypoperfusion (21, 22). Maintaining appropriate blood pressure and cerebral perfusion was necessary to alleviate secondary brain injury in TBI patients. A previous study including pediatric TBI patients illustrated that patients with poor outcomes had a higher base deficit level than those with good outcomes (12). Our results were similar to the findings of a previous study that indicated that non-survivors had a higher base deficit level than survivors. Another study showed that the base deficit on admission was statistically negatively correlated with GCS and RTS in adult TBI patients (24). However, the level of base deficit did not significantly differ between survivors and non-survivors in this study. This contradictory and unconvincing result might be attributable to the small sample size of this study. Although statistically non-significant after adjusting confounders, the base deficit was significantly related to in-hospital mortality in the univariate logistic regression analysis of our study.

It was estimated that a quarter of patients with severe trauma would present an abnormal blood coagulation test on admission, which would be positively associated with poor outcomes for these patients (25, 26). As a reflection of coagulation function, INR was confirmed as an accurate predictor of mortality and organ failure in trauma patients (27, 28). Acute traumatic coagulopathy (ATC) was primarily caused by the endothelial activation of the protein C pathway, which was induced by tissue injury and hypoperfusion (29, 30). Other factors such as resuscitation-induced hemodilution, hypothermia, and acidosis would aggravate the ATC (26, 31).

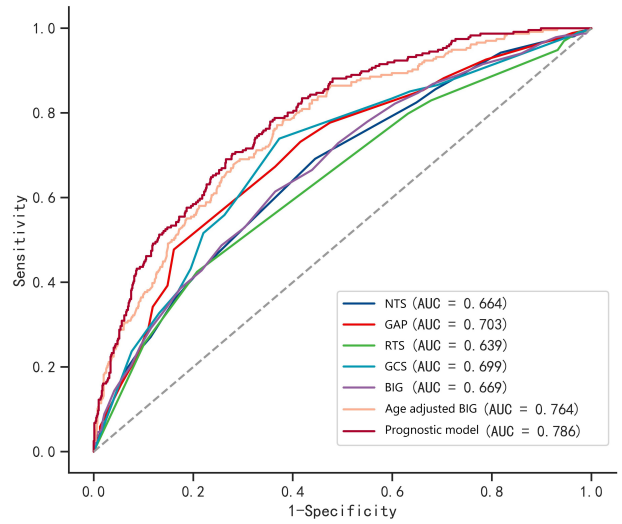

FIGURE 3
ROC curves of the BIG score, age-adjusted BIG score, other trauma triage scores, and constructed prognostic model. The constructed prognostic model is composed of age, SpO_2, glucose, hemoglobin, BIG, subarachnoid hemorrhage, and intracerebral hematoma.

The prevalence of coagulopathy after TBI had been reported as ranging from 7 to 63%. The huge discrepancy might be attributable to the different definitions of coagulopathy and heterogeneous populations (32–35). Specifically, the TBI itself was independently correlated with the development of coagulopathy due to the excessive fibrinolysis caused by extensive tissue factor release from the injured brain (36, 37). Coagulopathy was acknowledged as an independent risk factor of mortality and neurological outcomes in TBI patients (38–41). Poor coagulation function could increase the potential of intracranial hemorrhage, extracranial hemorrhage, and secondary neuronal loss (26, 36). Some studies indicated that incorporating results of the coagulation test including INR could improve the value of the conventional TBI prognostic model (42, 43). Therefore, the BIG score incorporating INR could reflect the severity and possible progression of TBI patients more comprehensively.

GCS, which has been widely used for nearly five decades, is an indicator of brain injury severity and cerebral perfusion. However, the classic GCS could not be accurately evaluated in intubated, sedated, and intoxicated patients (44, 45). The comparison of the AUC value between the GCS score alone and our age-adjusted BIG score showed that incorporating base deficit, INR, and age into GCS could improve the prognostic value and stability of clinical use in TBI patients. The multivariable prognostic model we constructed was composed of seven factors, namely, age, SpO_2, glucose, hemoglobin, BIG score, subarachnoid hemorrhage, and intracerebral hematoma. Although this model had a significantly higher AUC value than the age-adjusted BIG score, its evaluation was much more complex than the age-adjusted BIG score, which makes it more applicable in hospitalization but not in the emergency department. Instead, the simplicity and easy availability of the age-adjusted BIG score allow it to be quickly evaluated without the consideration of additional factors. This advantage is significant for physicians carrying out patient triage and providing intensive medical therapy for potentially high-risk TBI patients in the early stage after injury. Therefore, the age-adjusted BIG score has been specially applied by emergency department workers.

There were several limitations in this study. First, most of the included patients were those who received treatment in the ICU of a single medical center. Patients with mild TBI might not be included in this study. Nearly half of TBI patients in the database who did not meet inclusion criteria were excluded. Therefore, selection bias could not be avoided. The exact predictive value of the age-adjusted BIG score and the constructed prognostic model should be externally verified by a prospective study in other medical centers. Second, the predictive value of the age-adjusted BIG score was not specifically analyzed in subgroups of included TBI patients, such as patients with a penetrating injury or blunt injury. A previous study showed that the BIG score was more valuable in predicting outcomes of penetrating trauma patients than blunt trauma patients (14). Third, the level of base deficit and INR in admission could be influenced by pre-hospital intubation and resuscitation. Records of these two variables were not collected in the present study. Finally, in addition to RTS, other complex trauma scores such as ISS and TRISS were not evaluated in the present study. A study comparing the predictive value between age-adjusted BIG scores and these scores is worthwhile to conduct in the future. Despite these limitations, the readily available age-adjusted BIG score is more efficient than other complex scores in patient triage and treatment decisions in the early stage after brain injury.

Conclusion

As a pediatric trauma score, the BIG score is not applicable to adult TBI patients. However, the age-adjusted BIG score is a readily available and effective score that is beneficial for clinicians to triage adult TBI patients and evaluate possible progression in the early stage after injury. The prognostic model incorporating the BIG score has a better predictive value and could be used in TBI patients during hospitalization.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the West China Hospital of Sichuan University (NO: 2021-1684). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the

requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this observational study was performed using data from the Multiparameter Intelligent Monitoring in Intensive Care Database III (MIMIC-III database). All data of participants in this public database were deidentified and anonymized.

Author contributions

XB: Conceptualization, Data curation, Methodology, Resources, Software, Validation, Writing—original draft, Writing—review & editing. RW: Conceptualization, Data curation, Methodology, Resources, Software, Validation, Writing—original draft, Writing—review & editing. CZ: Investigation, Methodology, Project administration, Writing—original draft. DW: Formal analysis, Methodology, Resources, Supervision, Validation, Writing—review & editing. LM: Data curation, Formal analysis, Methodology, Resources, Supervision, Visualization, Writing—review & editing. MH: Data curation, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing—review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg.* (2018) 130:1080–97. doi: 10.3171/2017.10.JNS17352

2. Champion HR, Sacco WJ, Carnazzo AJ, Copes W, Fouty WJ. Trauma score. *Crit Care Med.* (1981) 9:672–6. doi: 10.1097/00003246-198109000-00015

3. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma.* (1974) 14:187–96. doi: 10.1097/00005373-197403000-00001

4. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. *Trauma Score Inj Severity Score.* (1987) 27:370–8. doi: 10.1097/00005373-198704000-00005

5. Champion HR, Sacco WJ, Hannan DS, Lepper RL, Atzinger ES, Copes WS, et al. Assessment of injury severity: the triage index. *Crit Care Med.* (1980) 8:201–8. doi: 10.1097/00003246-198004000-00001

6. Perel P, Arango M, Clayton T, Edwards P, Komolafe E, Poccock S, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ.* (2008) 336:425–9. doi: 10.1136/bmj.39461.643438.25

7. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med.* (2008) 5:e165. doi: 10.1371/journal.pmed.0050165

8. Borgman MA, Maegele M, Wade CE, Blackbourne LH, Spinella PC. Pediatric trauma BIG score: predicting mortality in children after military and civilian trauma. *Pediatrics.* (2011) 127:e892–7. doi: 10.1542/peds.2010-2439

9. El-Gamasy MA, Elezz AA, Basuni AS, Elrazek ME. Pediatric trauma BIG score: predicting mortality in polytraumatized pediatric patients. *Ind J Crit Care Med.* (2016) 20:640–6. doi: 10.4103/0972-5229.194011

10. Muisyo T, Bernardo EO, Camazine M, Colvin R, Thomas KA, Borgman MA, et al. Mortality prediction in pediatric trauma. *J Pediatr Surg.* (2019) 54:1613–6. doi: 10.1016/j.jpedsurg.2018.08.045

11. Grandjean-Blanchet C, Emeriaud G, Beaudin M, Gravel J. Retrospective evaluation of the BIG score to predict mortality in pediatric blunt trauma. *CJEM.* (2018) 20:592–9. doi: 10.1017/cem.2017.379

12. Davis AL, Hochstadter E, Daya T, Kulkarni AV, Wales P, Stephens D, et al. The base deficit, international normalized ratio, and Glasgow Coma Scale (BIG) score, and functional outcome at hospital discharge in children with traumatic brain injury. *Pediatr Crit Care Med.* (2019) 20:970–9. doi: 10.1097/PCC.0000000000002050

13. Holcomb JB, McMullin NR, Pearse L, Caruso J, Wade CE, Oetjen-Gerdes L, et al. Causes of death in U.S. special operations forces in the global war on terrorism: 2001-2004. *Ann Surg.* (2007) 245:986–91. doi: 10.1097/01.sla.0000259433.03754.98

14. Brockamp T, Maegele M, Gaarder C, Goslings JC, Cohen MJ, Lefering R, et al. Comparison of the predictive performance of the BIG, TRISS, and PS09 score in an adult trauma population derived from multiple international trauma registries. *Crit Care.* (2013) 17:R134. doi: 10.1186/cc12813

15. Jeong JH, Park YJ, Kim DH, Kim TY, Kang C, Lee SH, et al. The new trauma score (NTS): a modification of the revised trauma score for better trauma mortality prediction. *BMC Surg.* (2017) 17:77. doi: 10.1186/s12893-017-0272-4

16. Hasler RM, Mealing N, Rothen HU, Coslovsky M, Lecky F, Jüni P. Validation and reclassification of MGAP and GAP in hospital settings using data from the Trauma Audit and Research Network. *J Trauma Acute Care Surg.* (2014) 77:757–63. doi: 10.1097/TA.0000000000000452

17. Randolph LC, Takacs M, Davis KA. Resuscitation in the pediatric trauma population: admission base deficit remains an important prognostic indicator. *J Trauma.* (2002) 53:838–42. doi: 10.1097/00005373-200211000-00006

18. Hindy-François C, Meyer P, Blanot S, Marqué S, Sabourdin N, Carli P, et al. Admission base deficit as a long-term prognostic factor in severe pediatric trauma patients. *J Trauma.* (2009) 67:1272–7. doi: 10.1097/TA.0b013e31819db828

19. Kincaid EH, Chang MC, Letton RW, Chen JG, Meredith JW. Admission base deficit in pediatric trauma: a study using the National Trauma Data Bank. *J Trauma.* (2001) 51:332–5. doi: 10.1097/00005373-200108000-00018

20. Hodgman EI, Morse BC, Dente CJ, Mina MJ, Shaz BH, Nicholas JM, et al. Base deficit as a marker of survival after traumatic injury: consistent across changing patient populations and resuscitation paradigms. *J Trauma Acute Care Surg.* (2012) 72:844–51. doi: 10.1097/TA.0b013e31824ef9d2

21. Rixen D, Raum M, Bouillon B, Lefering R, Neugebauer E. Base deficit development and its prognostic significance in posttrauma critical illness: an analysis by the trauma registry of the Deutsche Gesellschaft für unfallchirurgie. *Shock.* (2001) 15:83–9. doi: 10.1097/00024382-200115020-00001

22. Davis JW, Parks SN, Kaups KL, Gladen HE, O'Donnell-Nicol S. Admission base deficit predicts transfusion requirements and risk of complications. *J Trauma.* (1996) 41:769–74. doi: 10.1097/00005373-199611000-00001

23. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg.* (2007) 245:812–8. doi: 10.1097/01.sla.0000256862.79374.31

24. Shallwani H, Waqas M, Waheed S, Siddiqui M, Froz A, Bari ME. Does base deficit predict mortality in patients with severe traumatic brain injury? *Int J Surg.* (2015) 22:125–30. doi: 10.1016/j.ijsu.2015.05.054

25. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J Trauma.* (2003) 55:39–44. doi: 10.1097/01.TA.0000075338.21177.EF

26. Whittaker B, Christiaans SC, Altice JL, Chen MK, Bartolucci AA, Morgan CJ, et al. Early coagulopathy is an independent predictor of mortality in children after severe trauma. *Shock.* (2013) 39:421–6. doi: 10.1097/SHK.0b013e31828e08cb

27. Verma A, Kole T. International normalized ratio as a predictor of mortality in trauma patients in India. *World J Emerg Med.* (2014) 5:192–5. doi: 10.5847/wjem.j.issn.1920-8642.2014.03.006

28. Peltan ID, Vande Vusse LK, Maier RV, Watkins TR. An international normalized ratio-based definition of acute traumatic coagulopathy is associated with mortality, venous thromboembolism, and multiple organ failure after injury. *Crit Care Med.* (2015) 43:1429–38. doi: 10.1097/CCM.0000000000000981

29. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: a review of mechanisms. *J Trauma.* (2008) 65:748–54. doi: 10.1097/TA.0b013e3181877a9c

30. Cohen MJ, Call M, Nelson M, Calfee CS, Esmon CT, Brohi K, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann Surg.* (2012) 255:379–85. doi: 10.1097/SLA.0b013e318235d9e6

31. Fries D, Innerhofer P, Schobersberger W. Time for changing coagulation management in trauma-related massive bleeding. *Curr Opin Anaesthesiol.* (2009) 22:267–74. doi: 10.1097/ACO.0b013e32832678d9

32. Joseph B, Aziz H, Zangbar B, Kulvatunyou N, Pandit V, O'Keeffe T, et al. Acquired coagulopathy of traumatic brain injury defined by routine laboratory tests: which laboratory values matter? *J Trauma Acute Care Surg.* (2014) 76:121–5. doi: 10.1097/TA.0b013e3182a9cc95

33. Laroche M, Kutcher ME, Huang MC, Cohen MJ, Manley GT. Coagulopathy after traumatic brain injury. *Neurosurgery.* (2012) 70:1334–45. doi: 10.1227/NEU.0b013e31824d179b

34. Maegele M, Schöchl H, Menovsky T, Maréchal H, Marklund N, Buki A, et al. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. *Lancet Neurol.* (2017) 16:630–47. doi: 10.1016/S1474-4422(17)30197-7

35. Maegele M, Aversa J, Marsee MK, McCauley R, Chitta SH, Vyakaranam S, et al. Changes in coagulation following brain injury. *Semin Thromb Hemost.* (2020) 46:155–66. doi: 10.1055/s-0040-1702178

36. Takayama W, Endo A, Koguchi H, Murata K, Otomo Y. Age-related differences in the impact of coagulopathy in patients with isolated traumatic brain injury: an observational cohort study. *J Trauma Acute Care Surg.* (2020) 89:523–8. doi: 10.21203/rs.2.19876/v1

37. Samuels JM, Moore EE, Silliman CC, Banerjee A, Cohen MJ, Ghasabyan A, et al. Severe traumatic brain injury is associated with a unique coagulopathy phenotype. *J Trauma Acute Care Surg.* (2019) 86:686–93. doi: 10.1097/TA.0000000000002173

38. James V, Chong SL, Shetty SS, Ong GY. Early coagulopathy in children with isolated blunt head injury is associated with mortality and poor neurological outcomes. *J Neurosurg Pediatr.* (2020) 25:663–9. doi: 10.3171/2019.12.PEDS19531

39. van Gent GAN, van Essen TA, Bos MHA, Cannegieter SC, van Dijck J, Peul WC. Coagulopathy after hemorrhagic traumatic brain injury, an observational study of the incidence and prognosis. *Acta Neurochir.* (2020) 162:329–36. doi: 10.1007/s00701-019-04111-z

40. Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study. *J Trauma.* (2009) 66:55–61. doi: 10.1097/TA.0b013e318190c3c0

41. Folkerson LE, Sloan D, Davis E, Kitagawa RS, Cotton BA, Holcomb JB, et al. Coagulopathy as a predictor of mortality after penetrating traumatic brain injury. *Am J Emerg Med.* (2018) 36:38–42. doi: 10.1016/j.ajem.2017.06.057

42. Yuan Q, Yu J, Wu X, Sun YR Li ZQ, Du ZY, et al. Prognostic value of coagulation tests for in-hospital mortality in patients with traumatic brain injury. *Scand J Trauma Resusc Emerg Med.* (2018) 26:3. doi: 10.1186/s13049-017-0471-0

43. Solla DJF, de Amorim RLO, Kolias AG, Hutchinson PJ, de Andrade AF, Teixeira MJ, et al. Incremental prognostic value of coagulopathy in addition to the crash score in traumatic brain injury patients. *Neurocrit Care.* (2020) 34:130–8. doi: 10.1007/s12028-020-00991-7

44. Ghaffarpasand F, Razmkon A, Dehghankhalili M. Glasgow Coma Scale score in pediatric patients with traumatic brain injury; limitations and reliability. *Bull Emerg Trauma.* (2013) 1:135–6.

45. Zuercher M, Ummenhofer W, Baltussen A, Walder B. The use of Glasgow Coma Scale in injury assessment: a critical review. *Brain Inj.* (2009) 23:371–84. doi: 10.1080/02699050902926267

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Chronic kidney disease as a predictive factor for poor prognosis in traumatic brain injury among older adults: a case-control study

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Objective: Traumatic brain injury (TBI) is a highly prevalent neurological disorder that affects a gradually increasing proportion of older adults. Chronic kidney disease (CKD) significantly contributes to global years of life lost, with an estimated one-tenth of the global population affected by CKD. However, it remains unclear whether CKD impacts TBI prognosis. We conducted a case-control study to investigate the clinical outcomes of TBI patients with or without CKD comorbidity and identified the risk factors associated with a poor prognosis.

Methods: From January 2017 through April 2023, 11 patients with TBI and CKD were included, and 27 control TBI cases with normal kidney function were matched by age, gender, and admission Glasgow Coma Scale (GCS) score as the control group.

Results: The CKD TBI group had a significantly lower GCS score upon discharge (7.1 ± 5.9) compared to the non-CKD TBI group (13.1 ± 2.6) ($p < 0.01$). ICU stay time and hospitalization expenses were higher in the CKD group than the non-CKD group, though there were no statistical differences. Additionally, patients in the CKD TBI group had a higher frequency of hospital-acquired infections (54.4%) compared with those in the non-CKD TBI group (7.4%) ($p < 0.01$). The two groups exhibited no differences in hemoglobin levels, albumin levels, or coagulation function. Logistic regression analysis showed that advanced age, low admission GCS score, elevated blood urea, and creatinine levels were associated with a poor neurological prognosis.

Conclusion: TBI patients comorbid with CKD have a poorer prognosis than those with normal kidney function.

KEYWORDS

traumatic brain injury, clinical research, prognosis, chronic kidney disease, glasgow coma scale score, serum creatine

1 Introduction

Traumatic brain injury (TBI) is a highly prevalent neurological disorder that is impacting a gradually increasing proportion of elderly patients. Falls and road traffic accidents are the leading causes of TBI. The acute injury caused by TBI and the ensuing long-term functional impairments that present themselves during rehabilitation significantly burden patients' health (1–3). Chronic kidney disease (CKD) is a significant contributor to global years of life lost, and an estimated one-tenth of the global population may be affected by CKD. The rising prevalence of chronic conditions such as diabetes, hypertension, and obesity elevates the magnitude of CKD as a pressing public health concern (4–6).

A growing amount of attention is being given to brain-kidney interactions, and some studies have explored the association between TBI and kidney dysfunction, with the majority of the research focusing on the relationship between TBI and post-traumatic acute kidney injury (AKI) (7, 8). Although the mechanisms are not fully understood, potential factors contributing to TBI-induced AKI include post-injury inflammation and the dysregulation of catecholamine release (9). Wu et al. reported that an increased risk of long-term CKD development was associated with TBI (10). However, it remains unclear whether CKD impacts TBI prognosis. Therefore, we conducted a case-control study to investigate the clinical outcomes of older TBI patients comorbid with CKD and identified the risk factors associated with a poor prognosis.

2 Methods

This retrospective case-control study did not involve traceable personal information, and patient consent was not required. The ethics committee of Xiangya Hospital, Central South University, approved the study. This study was reported following guidelines written according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (11).

2.1 Participants

From January 2017 through April 2023, brain injury patients admitted to Xiangya Hospital of Central South University were included in the trial if they had traumatic brain injury, were aged ≥65 years old, and had CKD [eGFR < 60 mL/(min·1.73 m^2) lasting for at least 3 months].

2.2 Data collection

The medical records and relevant examination data of the included patients were retrieved from our medical center's electronic medical record system. The demographic data included the patients' age, gender, admission Glasgow Coma Scale (GCS) score, mechanism of injury, lesions of injuries, and history of pre-existing chronic diseases. After reviewing each patient's computed tomography (CT) scan data, we documented radiological features such as epidural hematoma, subdural hematoma, cerebral contusion, and other relevant findings. The biochemical parameters of the patients mainly included the initial admission levels of hemoglobin (Hb), albumin (Alb), serum urea, serum creatinine (Cr), coagulation function parameters, and etiological culture results.

2.3 Outcomes

The primary outcomes included the patients' discharge GCS score, infection status during hospitalization, number of days of hospital stay, number of days of intensive care unit (ICU) stay, and hospitalization expenses. The secondary outcome measure was the difference in discharge and admission GCS scores. If the discharge GCS score was lower than the admission GCS score, the patient was defined as having an unfavorable outcome.

2.4 Statistical analysis

Categorical data are presented as counts and percentages, and continuous data are expressed as mean ± standard deviation or median (interquartile range). A comparison between categorical data was performed using the chi-square test, and continuous data were compared using the *t*-test or non-parametric tests.

To investigate the relative risk of potential predictor variables, univariate logistic regression was applied to obtain the odds ratios (ORs) and 95% confidence intervals (CIs). Based on the significant factors identified in the univariate analysis, a receiver operating characteristic (ROC) curve model was established. The model's discriminatory power was evaluated by calculating the area under the curve (AUC) of the ROC curve. The cutoff value was determined by maximizing the Youden index in the ROC curve analysis. A p-value of < 0.05 was considered statistically significant. All data analysis was performed using R version 4.1.0.

3 Results

3.1 Patient inclusion and characteristics

From January 2017 through April 2023, 1,736 brain injury patients were admitted to Xiangya Hospital of Central South University. Of these, 289 cases of chronic subdural hematoma, 1,120 cases under the age of 65, and 10 cases of AKI were excluded. Finally, 11 cases of TBI comorbid with CKD were screened (CKD TBI group). A total of 27 TBI patients with normal kidney function were matched for age, gender, and admission GCS scores and included in the control group (non-CKD TBI group) (Figure 1).

A total of 38 TBI patients were analyzed. Table 1 presents their baseline characteristics. The average age of the 38 patients was 70.5 ± 4.5 years, and there were 31 males (81.6%) (Table 1). The GCS score on admission was 11.6 ± 2.7. Falling was the most common mechanism of injury, accounting for 47.4% of all injuries. Other mechanisms included traffic accidents (36.8%) and assaults (5.3%). Imaging examinations revealed intracranial lesions, including epidural hematoma (13.2%),

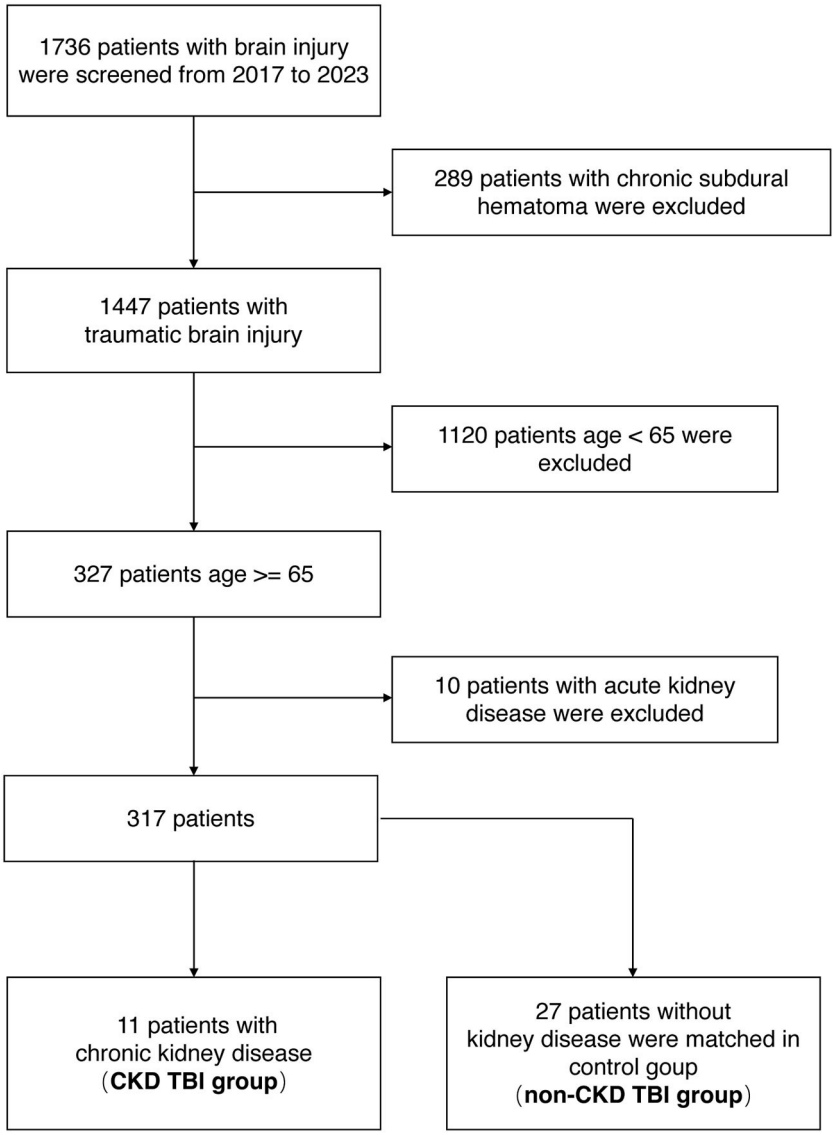

FIGURE 1
Flowchart for selection of analyzed participants.

subdural hematoma (55.3%), and cerebral contusion (65.8%) (Table 1).

Patients in the CKD TBI group had a higher frequency of comorbidities such as hypertension, diabetes, and coronary heart disease ($p < 0.05$) (Table 1). We also recorded detailed laboratory markers upon the patients' admission. The average values for Hb and Alb were 108.8 g/L and 32.9 g/L, respectively. The patients in the CKD TBI group had lower levels of Hb and Alb compared to the non-CKD TBI group, although the differences were not statistically significant. There was no difference in coagulation function between the two groups. Regarding renal function markers, patients from the CKD TBI group showed significantly higher levels of serum urea (18.2 ± 10.9 mmol/L) and serum creatinine (307.1 ± 197.5 μmol/L) than patients from the non-CKD TBI group, with values of 5.0 ± 1.4 mmol/L and 75.9 ± 13.6 μmol/L, respectively ($p < 0.01$) (Table 1).

3.2 Clinical outcomes

Next, we compared the overall outcomes of the two patient groups upon discharge (Table 2). It is worth noting that the patients from the CKD TBI group had a significantly lower GCS scores upon discharge (7.1 ± 5.9) compared with the non-CKD TBI group (13.1 ± 2.6) ($p < 0.01$). The median length of hospital stay was comparable between the two groups. Patients in the CKD TBI group spent longer in the ICU, and their overall hospitalization costs were higher than those of the non-CKD TBI group. However, the differences were not statistically significant.

Additionally, patients in the CKD TBI group had a higher frequency of hospital-acquired infections (54.4%) compared with the non-CKD TBI group (7.4%) ($p < 0.01$) (Table 2). Four patients in the CKD TBI group experienced multi-species and multi-site infections with various pathogens, including gram-negative

TABLE 1 Baseline characteristics of included patients.

	ALL	Non-CKD	CKD	*P* value
	N = 38	*N* = 27	*N* = 11	
Age (y)	70.5 (4.5)	69.7 (4.3)	72.5 (4.7)	0.107
Sex, *n* (%)				0.648
Female	7 (18.4)	6 (22.2)	1 (9.1)	
Male	31 (81.6)	21 (77.8)	10 (90.9)	
GCS admission	11.6 (2.7)	12.1 (2.5)	10.5 (3.0)	0.126
Mechanism, *n* (%)				0.938
Traffic accident	14 (36.8)	10 (37.0)	4 (36.4)	
Falling	18 (47.4)	13 (48.1)	5 (45.5)	
Assault	2 (5.3)	1 (3.7)	1 (9.1)	
Other	4 (10.5)	3 (11.1)	1 (9.1)	
Location of lesions, *n* (%)				
EDH	5 (13.2)	4 (14.8)	1 (9.1)	1.000
SDH	21 (55.3)	13 (48.1)	8 (72.7)	0.282
Cerebral contusion	25 (65.8)	17 (63.0)	8 (72.7)	0.714
Medical history, *n* (%)				
Hypertension	21 (55.3)	11 (40.7)	10 (90.9)	0.010
Diabetes	6 (15.8)	1 (3.7)	5 (45.5)	0.005
CHD	10 (26.3)	3 (11.1)	7 (63.6)	0.002
Stroke	2 (5.3)	2 (7.4)	0 (0.0)	1.000
Hb (g/L)	108.8 (22.2)	110.2 (22.9)	105.2 (20.7)	0.517
Alb (g/L)	32.9 (5.7)	33.2 (6.0)	32.3 (5.1)	0.645
Urea (mmol/L)	8.8 (8.4)	5.0 (1.4)	18.2 (10.9)	0.002
Cr (μmol/L)	142.8 (148.2)	75.9 (13.6)	307.1 (197.5)	0.003
PT, *n* (%)				0.295
Long	5 (13.5)	5 (19.2)	0 (0.0)	
Normal	32 (86.5)	21 (80.8)	11 (100.0)	
APTT, *n* (%)				0.540
Long	3 (8.1)	3 (11.5)	0 (0.0)	
Normal	34 (91.9)	23 (88.5)	11 (100.0)	

CKD, chronic kidney disease; GCS, glasgow coma scale; EDH, epidural hematoma; SDH, subdural hematoma; CHD, coronary heart disease; Hb, hemoglobin; Alb, albumin; Cr, creatinine; PT, prothrombin time; APTT, activated partial thromboplastin time.

TABLE 2 Comparison of clinical outcomes between TBI patients with CKD and without CKD.

	ALL *N* = 38	Non-CKD *N* = 27	CKD *N* = 11	*P* value
Hospital stay (days)	14.0 (9.0, 19.8)	14.0 (9.5, 18.5)	13.0 (7.5, 29.0)	0.847
ICU stay (days)	3.0 (0.0, 12.8)	3.0 (0.0, 9.5)	10.0 (1.0, 29.0)	0.115
Cost (¥)	113,358.9 (43,541.0, 154,290.8)	110,152.7 (39,286.9, 132,064.2)	146,633.3 (48,707.2, 361,544.5)	0.111
GCS discharge	11.4 (4.7)	13.1 (2.6)	7.1 (5.9)	0.007
Infection, *n* (%)				0.004
No	30 (78.9)	25 (92.6)	5 (45.5)	
Yes	8 (21.1)	2 (7.4)	6 (54.5)	

CKD, chronic kidney disease; ICU, intensive care unit; GCS, glasgow coma scale.

bacteria, gram-negative cocci, and fungi. The most common site of infection was the lungs, followed by the urinary tract and central nervous system.

Furthermore, we conducted linear regression analysis on both groups' admission and discharge GCS scores (Figure 2). The CKD TBI group showed a fitted curve with an R-value of 0.93 ($p < 0.001$), while the non-CKD TBI group had a fitted curve with an R-value of 0.49 ($p < 0.01$). Among the TBI patients with lower admission GCS scores, those with comorbid CKD had lower GCS scores upon discharge than those without CKD. Conversely, for patients in both groups with higher admission GCS scores, higher GCS scores were observed upon discharge.

3.3 Association of renal indicators with outcomes

After defining a discharge GCS score lower than the admission GCS score as a indicator of an unfavorable outcome, we calculated the ORs for the relevant indicators in univariate logistic models for adverse prognostic outcomes (Table 3). Advanced age upon admission, low admission GCS score, and high levels of initial serum urea and serum creatinine were closely associated with poor TBI outcomes.

Next, we constructed ROC curves to explore the ability of serum urea and serum creatinine to predict adverse outcomes in TBI (Figure 3). The results indicated that serum urea and serum creatinine can be used to predict poor prognostic outcomes in TBI, with AUCs of 0.877 and 0.828, respectively. The optimal cutoff values for serum urea and creatinine were 10.97 (mmol/L) and 129.50 (μmol/L), respectively.

4 Discussion

Aging is a global problem, and TBI has become increasingly prevalent among older adults (12). With the increase in the prevalence of chronic diseases such as diabetes in adults, the burden of renal failure is also increasing (13). This case-control study analyzed the clinical outcomes and risk factors of TBI patients with CKD comorbidity. Among cases with similar severity of brain injury, TBI patients with concurrent CKD generally exhibited poorer outcomes compared to the general TBI population.

TBI patients with concurrent CKD constitute a high-risk population in neurointensive care and require special attention from treating physicians. Our study identified urea and creatinine as serum biomarkers that can be used to predict adverse outcomes in TBI events. As renal function progressively declines, CKD

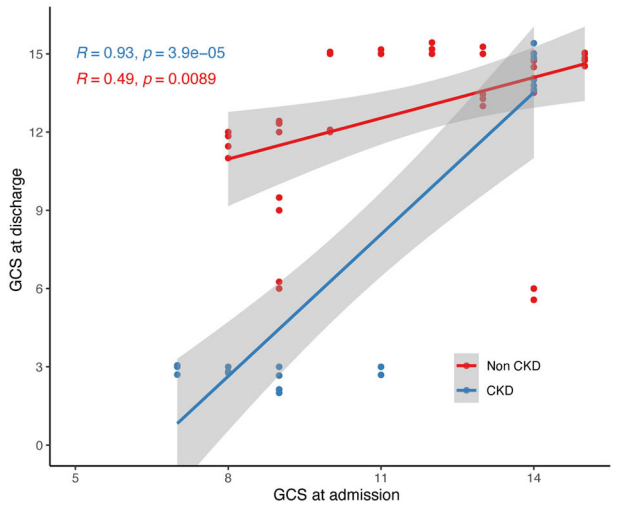

FIGURE 2
Linear regression of admission and discharge GCS scores of two group of participants. GCS, glasgow coma scale.

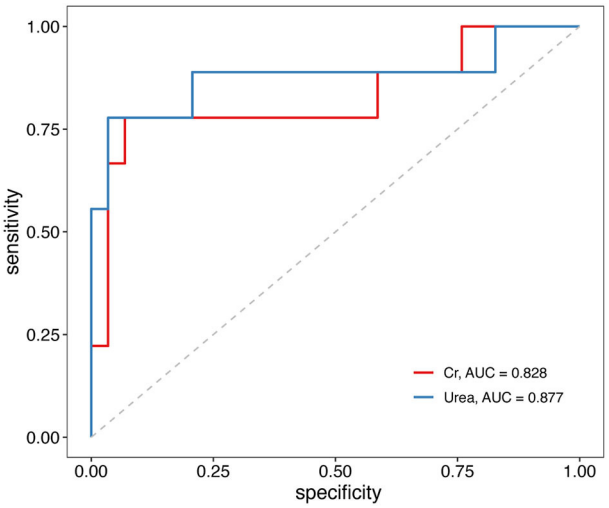

FIGURE 3
Receiver operating characteristic (ROC) curves of serum urea and creatinine associations with unfavorable outcomes in TBI patients. TBI, traumatic brain injury.

TABLE 3 Univariate logistic regression for independent variables related to poor outcomes.

	OR (95% CI)	*P* value
Age	1.30 (1.06, 1.60)	0.013
GCS admission	0.56 (0.37, 0.85)	0.006
Urea	1.47 (1.12, 1.93)	0.006
Cr	1.01 (1.00, 1.02)	0.017

OR, odds ratio; GCS, glasgow coma scale; Cr, creatinine.

patients may experience various complications such as anemia, malnutrition, and coagulation dysfunction (6). However, when we compared hemoglobin levels, serum albumin levels, and coagulation function indexes between the CKD TBI group and the non-CKD TBI group in this study, there were no statistical differences between the two groups, and logistic regression did not indicate that these indexes affect the prognosis of TBI patients.

This study found that patients with TBI comorbid with CKD had a higher prevalence of chronic diseases, such as hypertension, diabetes, and coronary heart disease. These diseases can cause arteriosclerosis or worse vascular conditions, which may be related to a worse prognosis for TBI patients with CKD (14, 15). In addition, CKD patients tend to have internal environment disorders such as azotemia. The accumulation of various metabolic substances in CKD may exacerbate the severity of brain injury in TBI patients (16, 17). For instance, guanidine compounds, a group of uremic neurotoxins, have neurotoxic and vascular toxic effects on neurons and blood vessels (18). Another uremic neurotoxin, asymmetric dimethylarginine, may affect cerebral blood flow and decrease cerebral perfusion (19). Azotemia in CKD patients can also exacerbate brain injury, which manifests as an aggravation of post-traumatic brain edema by disrupting the blood-brain barrier via osmotic pressure disturbances.

CKD patients are prone to infection. As CKD is a systemic disease, prolonged energy insufficiency, the accumulation of various inflammatory mediators, and the dysregulation of the autonomic nervous system may attenuate immunity in patients (20, 21). In this study, we observed a significantly higher incidence of infection in TBI patients with comorbid CKD compared to the non-CKD group. Moreover, multiple pathogens and multiple site infections were more common in TBI patients comorbid with CKD and may lead to a prolonged ICU stay and increased hospitalization costs. Therefore, doctors need to monitor for infection in TBI patients comorbid with CKD and be alert to hospital-acquired infections.

There were several limitations in our study. Firstly, this study was inherently a single-center retrospective case-control study with a relatively small number of patients included, which may restrict the generalizability of our conclusions. Therefore, caution should be exercised when extending our findings to a broader population. Further validation of our findings is warranted through prospective studies based on larger cohorts. Secondly, due to limitations in the original medical records data, we used the discharge GCS score as the outcome measure, but data on the long-term prognosis of patients after discharge should be collected as further evaluation criteria. Thirdly, it is worth noting that other underlying comorbidities in the elderly population may act as confounding factors that influence the interpretation of our results. Future research should consider incorporating additional relevant factors in the case matching process.

In summary, TBI patients comorbid with CKD have a poorer prognosis than those with normal kidney function. Elevated serum urea and creatine levels are considered risk factors for poorer clinical prognosis in older TBI patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Xiangya Hospital, Central South University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HM: Data curation, Formal analysis, Funding acquisition, Visualization, Writing – original draft. FF: Data curation, Formal analysis, Project administration, Resources, Writing – review & editing. JL: Data curation, Formal analysis, Writing – review & editing. WZ: Data curation, Formal analysis, Writing – review & editing. QW: Writing – review & editing. XY: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Stocchetti N, Zanier ER. Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Crit Care.* (2016) 20:148. doi: 10.1186/s13054-016-1318-1

2. Roozenbeek B, Maas AIR, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol.* (2013) 9:231–6. doi: 10.1038/nrneurol.2013.22

3. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. *Med Clin North Am.* (2020) 104:213–38. doi: 10.1016/j.mcna.2019.11.001

4. Coresh J. Update on the burden of CKD. *JASN.* (2017) 28:1020–2. doi: 10.1681/ASN.2016121374V

5. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nat Rev Nephrol.* (2017) 13:104–14. doi: 10.1038/nrneph.2016.163

6. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management. *JAMA.* (2019) 322:1294. doi: 10.1001/jama.2019.14745

7. Udy AA, Jarrett P, Lassig-Smith M, Stuart J, Starr T, Dunlop R, et al. Augmented renal clearance in traumatic brain injury: a single-center observational study of atrial natriuretic peptide, cardiac output, and creatinine clearance. *J Neurotrauma.* (2017) 34:137–44. doi: 10.1089/neu.2015.4328

8. Barea-Mendoza JA, Chico-Fernández M, Quintana-Díaz M, Serviá-Goixart L, Fernández-Cuervo A, Bringas-Bollada M, et al. Traumatic brain injury and acute kidney injury-outcomes and associated risk factors. *JCM.* (2022) 11:7216. doi: 10.3390/jcm11237216

9. De Vlieger G, Meyfroidt G. Kidney dysfunction after traumatic brain injury: pathophysiology and general management. *Neurocrit Care.* (2023) 38:504–16. doi: 10.1007/s12028-022-01630-z

10. Wu C-L, Kor C-T, Chiu P-F, Tsai C-C, Lian I-B, Yang T-H, et al. Long-term renal outcomes in patients with traumatic brain injury: A nationwide population-based cohort study. *PLoS ONE.* (2017) 12:e0171999. doi: 10.1371/journal.pone.0171999

11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* (2007) 370:1453–7. doi: 10.1016/S0140-6736(07)61602-X

12. Rauen K, Späni CB, Tartaglia MC, Ferretti MT, Reichelt L, Probst P, et al. Quality of life after traumatic brain injury: a cross-sectional analysis uncovers age- and sex-related differences over the adult life span. *GeroScience.* (2021) 43:263–78. doi: 10.1007/s11357-020-00273-2

13. Kelly DM, Anders H-J, Bello AK, Choukroun G, Coppo R, Dreyer G, et al. International Society of Nephrology Global Kidney Health Atlas: structures, organization, and services for the management of kidney failure in Western Europe. *Kidney Int Suppl.* (2021) 11:e106–18. doi: 10.1016/j.kisu.2021.01.007

14. Vervloet M, Cozzolino M. Vascular calcification in chronic kidney disease: different bricks in the wall? *Kidney Int.* (2017) 91:808–17. doi: 10.1016/j.kint.2016.09.024

15. Hobson S, Arefin S, Witasp A, Hernandez L, Kublickiene K, Shiels PG, et al. Accelerated vascular aging in chronic kidney disease: the potential for novel therapies. *Circ Res.* (2023) 132:950–69. doi: 10.1161/CIRCRESAHA.122.321751

16. Afsar B, Sag AA, Yalcin CE, Kaya E, Siriopol D, Goldsmith D, et al. Brain-kidney cross-talk: definition and emerging evidence. *Eur J Intern Med.* (2016) 36:7–12. doi: 10.1016/j.ejim.2016.07.032

17. Tanaka S, Okusa MD. Crosstalk between the nervous system and the kidney. *Kidney Int.* (2020) 97:466–76. doi: 10.1016/j.kint.2019.10.032

18. De Deyn PP, Vanholder R, D'Hooge R. Nitric oxide in uremia: effects of several potentially toxic guanidino compounds. *Kidney Int.* (2003) 63:S25–8. doi: 10.1046/j.1523-1755.63.s84.9.x

19. Kielstein JT, Donnerstag F, Gasper S, Menne J, Kielstein A, Martens-Lobenhoffer J, et al. Increases arterial stiffness and decreases cerebral blood flow in humans. *Stroke.* (2006) 37:2024–9. doi: 10.1161/01.STR.0000231640.32543.11

20. Zoccali C, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, et al. The systemic nature of CKD. *Nat Rev Nephrol.* (2017) 13:344–58. doi: 10.1038/nrneph.2017.52

21. Cheung WW, Paik KH, Mak RH. Inflammation and cachexia in chronic kidney disease. *Pediatr Nephrol.* (2010) 25:711–24. doi: 10.1007/s00467-009-1427-z

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Diffusion basis spectrum imaging detects subclinical traumatic optic neuropathy in a closed-head impact mouse model of traumatic brain injury

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Introduction: Traumatic optic neuropathy (TON) is the optic nerve injury secondary to brain trauma leading to visual impairment and vision loss. Current clinical visual function assessments often fail to detect TON due to slow disease progression and clinically silent lesions resulting in potentially delayed or missed treatment in patients with traumatic brain injury (TBI).

Methods: Diffusion basis spectrum imaging (DBSI) is a novel imaging modality that can potentially fill this diagnostic gap. Twenty-two, 16-week-old, male mice were equally divided into a sham or TBI (induced by moderate Closed-Head Impact Model of Engineered Rotational Acceleration device) group. Briefly, mice were anesthetized with isoflurane (5% for 2.5 min followed by 2.5% maintenance during injury induction), had a helmet placed over the head, and were placed in a holder prior to a 2.1-joule impact. Serial visual acuity (VA) assessments, using the Virtual Optometry System, and DBSI scans were performed in both groups of mice. Immunohistochemistry (IHC) and histological analysis of optic nerves was also performed after *in vivo* MRI.

Results: VA of the TBI mice showed unilateral or bilateral impairment. DBSI of the optic nerves exhibited bilateral involvement. IHC results of the optic nerves revealed axonal loss, myelin injury, axonal injury, and increased cellularity in the optic nerves of the TBI mice. Increased DBSI axon volume, decreased DBSI $\lambda_{||}$, and elevated DBSI restricted fraction correlated with decreased SMI-312, decreased SMI-31, and increased DAPI density, respectively, suggesting that DBSI can detect coexisting pathologies in the optic nerves of TBI mice.

Conclusion: DBSI provides an imaging modality capable of detecting subclinical changes of indirect TON in TBI mice.

KEYWORDS

traumatic optic neuropathy, traumatic brain injury, diffusion MRI, diffusion basis spectrum imaging, axonal loss, inflammation, modCHIMERA

Introduction

Traumatic brain injury (TBI) results in several, burdensome, ocular pathologies. A substantial proportion of patients with TBI experience visual problems resulting from optic neuropathy (1–5). Optic neuropathy in TBI can be direct or indirect. Direct traumatic optic neuropathy (TON) results from anatomical disruption of the optic nerve, whereas indirect TON originates from optic nerve stretch during a head injury. The latter can also occur due to secondary injury to the retinal ganglion cell axons (6, 7). Preclinical studies have showed that repeated mild TBI results in loss of the retinal nerve fiber layer and the inner plexiform layer (8–10). Changes in the pupillary diameter have also been noted following TBI, suggesting its neurovascular implications on the visual pathway in TBI (10). These changes may potentially root from a systemic and local dopaminergic disruption of the retina following TBI (10), and hemorrhage or edema (11–14). Both direct and indirect TON can contribute to optic nerve damage and a clear distinction is not always straightforward given that the optic nerve is vulnerable to multiple insults, such as the transmission of force or transient ischemia (12, 14).

TON is not commonly diagnosed due to slow disease progression, and undetected subclinical visual dysfunction. Missed diagnosis of indirect TON could lead to delayed or inappropriate treatment and subsequent reduction in visual function. Thus, an accurate and timely diagnosis of indirect TON is an unmet clinical need in treating patients with TBI. However, diagnosis of indirect TON is incomplete because standard visual functional assessments have limitations for appropriately reflecting optic nerve pathology (3, 15, 16). Tests such as optical coherence tomography (OCT) are also limited in detecting indirect TON as the accuracy of the retinal nerve fiber layer thickness can be confounded by inflammation-associated swelling in TBI (17). In addition, OCT cannot assess the posterior segment of the optic nerve, the most likely location of injury in indirect TON (12, 18).

To assess the posterior segment of the optic nerve, conventional magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) have seen increased application providing a comprehensive assessment of the visual system and related intracranial pathologies (19–21). However, both conventional MRI and DTI lack the needed specificity for the underlying pathologies in optic nerves (e.g., T2-hyperintense lesions can reflect demyelination, inflammation, or both, and changes in fractional anisotropy and apparent diffusion coefficient can result from axonal injury, demyelination, and/or inflammation) (20, 22–25).

To overcome the limitations of conventional MRI and DTI, diffusion basis spectrum imaging (DBSI) has been developed to detect, differentiate, and quantify coexisting pathologies (26), and to assess treatment efficacy (27, 28) in the optic nerve of a mouse model of multiple sclerosis. Aside from the application in optic nerve, DBSI has also demonstrated the ability to detect spinal cord axonal loss in patients with cervical spondylotic myelopathy (29, 30) and a mouse model of spinal cord injury (31) in the presence of tissue swelling. Thus, DBSI may hold the potential to specifically assess coexisting pathologies and reflect the corresponding severity of the underlying white-matter pathological components. In this study, DBSI was used to image the optic nerves of the murine moderate Closed-Head Impact Model of Engineered Rotational Acceleration (modCHIMERA) (32) to detect indirect TON and assess the progression of optic nerve pathology.

Methods

All experimental procedures were approved by the Washington University Institutional Animal Care and Use Committee (IACUC) and performed according to the Public Health Service Policy on Humane Care and Use of Laboratory Animals (33).

Experimental design

Twenty-two male C57BL/6 mice at age of 16 weeks old (The Jackson Laboratory, Bar Harbor, ME) were housed and maintained in the Washington University animal facility and subjected to a 12-h light/dark cycle. Eleven mice (five for *in vivo* and six for *ex vivo*) were injured as previously described using the modCHIMERA model (32). Briefly, mice were anesthetized with isoflurane (5% for 2.5 min followed by 2.5% maintenance during injury induction), had a helmet placed over the head, and were placed into a holder prior to a 2.1-joule impact (moderate—severe TBI) (32). The sham control group consisted of 11 (five for *in vivo* and six for *ex vivo*) mice undergoing the exact procedure without impact.

In vivo cohort (n = 5 for each group): Visual acuity assessment and DBSI scans were performed at 1, 3, 7, and 30 days after impact or sham operation. At the end of the DBSI time course, the TBI and sham mice were deeply anesthetized and underwent perfusion-fixation via the left cardiac ventricle with phosphate buffered saline (PBS), followed by 4% paraformaldehyde (PFA). Brains were excised and stored in 4% PFA at 4°C for 24 h and then transferred to PBS for paraffin embedding processing. *Ex vivo cohort (n = 6 for each group)*: 3 days after impact or sham operation, mice were perfusion-fixed with 4% paraformaldehyde in PBS. After removing the skull, brain specimens were left in 4% paraformaldehyde for overnight at 4°C and then transferred to a 3-ml syringe filling with PBS for the *ex vivo* scan. After the *ex vivo* scan, the batch of the *ex vivo* cohort was processed with the same paraffin embedding processing protocol as the *in vivo* cohort.

Visual acuity (for *in vivo* cohort only)

Mouse visual acuity (VA) was assessed using the Virtual Optometry System (Optometry, Cerebral Mechanics, Inc., Canada). Briefly, the virtual rotating columns were projected on the LCD monitors with different spatial frequencies in cycles/degree (c/d). The mouse head movement in response to the rotating virtual columns was noted. The VA was defined as the highest spatial frequency the mouse was able to respond to the virtual rotating columns. The spatial frequency was changed starting from 0.1 c/d with a step size of 0.05 c/d until the mouse stopped responding. When VA $\leq$ 0.25 c/d, the mouse was considered to develop impaired VA, as defined by previous studies (26, 27, 34, 35). VA was performed right before each *in vivo* MRI scan session.

Magnetic resonance imaging

In vivo and *ex vivo* magnetic resonance imaging (MRI) experiments were performed on a 4.7-T Agilent DirectDrive™ small-animal MRI system (Agilent Technologies, Santa Clara, CA) equipped with a Magnex/Agilent HD imaging gradient coil (Magnex/Agilent, Oxford, United Kingdom). *In vivo DBSI protocol*: Mice were anesthetized with

~1% isoflurane/oxygen during scans. Breathing rate was monitored and body temperature was maintained at 37° C with a small animal physiological monitoring and control unit (SA Instruments, Stony Brook, NY). An actively decoupled 1.7-cm receive coil (36) was placed on top of the mouse head for MR signal reception. The animal holder assembly, containing the receive coil and monitoring accessories, was placed inside an 8-cm actively decoupled volume transmit coil, in a 12-cm cradle to be placed inside the magnet. 25-direction diffusion-weighted measurements were performed by a multi-echo spin-echo diffusion-weighting imaging sequence (37) with the following parameters: repetition time (TR) = 1.5 s; echo time (TE) = 35 ms; inter-echo delay = 20.7 ms; field of view (FOV) = 22.5 × 22.5 mm^2; matrix size = 192 × 192 (zero-filled to 384 × 384), slice thickness = 1 mm, max; b value = 2,200 s/mm^2, Δ = 18 ms; δ = 6 ms; total scan time = 124 min (26). *Ex vivo DBSI protocol*: The sample syringe was inserted into the solenoid surface coil to cover the whole brain. 99-direction diffusion-weighted measurements were performed by a multi-echo spin-echo diffusion-weighting imaging sequence (37) with the following parameters: TR = 3.0 s, TE = 31.5 ms, inter-echo delay = 23.4 ms, Δ = 18 ms, δ = 6 ms, maximal b-value = 3,000 s/mm^2, with the same FOV = 15 × 15 mm^2, slice thickness = 1 mm, and matrix size = 128 × 128 (zero-filled to 256 × 256). Total scan time was 10 h and 33 min.

Imaging mouse optic nerve

The imaging site was at the pre-chiasmic segment of the optic nerve exhibiting symmetric left and right optic nerves in the axial view of the mouse brain. To maintain the consistency of imaging location, the multi-axial scout images were used to define mid-sagittal image slice (Supplementary Figure S1A). Mid-sagittal scout image with diffusion-weighting along the slice-selection direction was used to visualize corpus callosum (Supplementary Figure S1B, light blue arrow) and the optic nerve (Supplementary Figure S1B, green arrow). The reference axial image slice (Supplementary Figure S1B, red rectangle) was acquired perpendicular to the optic nerve, and the genu of corpus callosum was in the reference axial image slice (Supplementary Figure S1B, red rectangle). The cross-sectional optic nerves were at the final axial image with minimal confounding effects from cerebrospinal fluid (Supplementary Figure S1C).

Diffusion MRI data analysis

Diffusion-weighted (DW) data were denoised (38) and converted into nifti format. The nifti-format DW data were analyzed with a lab-developed DBSI software package to perform DBSI multi-tensor analysis (20, 39). For optic nerve white matter tracts (coherent fiber bundles), the diffusion-weighted imaging data was modeled according to Equation 1:

$$S_k = fe^{-\left|\overline{b_k}\right|\lambda_\perp} e^{-\left|\overline{b_k}\right|\left(\lambda_\parallel-\lambda_\perp\right)\cos^2\Phi_k} + \int_a^b f\left(D\right)e^{-\left|\overline{b_k}\right|D}dD \left(k=1,2,3,\ldots,25\right) \quad (1)$$

The quantities S_k and $\left|\overline{b_k}\right|$ are the signal and *b*-value of the k^{th} diffusion gradient; Φ_k is the angle between the k^{th} diffusion gradient and the principal direction of the anisotropic tensor; $\lambda_\parallel$ and $\lambda_\perp$ are the axial and radial diffusivities of the anisotropic tensor, respectively; f is the signal intensity fraction for the anisotropic tensor; *a* and *b* are the low and high diffusivity limits for the isotropic diffusion spectrum, reflecting cellularity and edema, respectively, $f\left(D\right)$. DBSI-derived f represents optic nerve white-matter tract density in an image voxel. DBSI-derived $\lambda_\parallel$ and $\lambda_\perp$ reflect residual axon and myelin integrity, respectively: ↓ $\lambda_\parallel \approx$ axonal injury and ↑ $\lambda_\perp \approx$ myelin damage (20, 39–41). As dictated by previous experimental findings, the restricted isotropic diffusion fraction reflecting cellularity in mouse optic nerves is derived by the summation of $f\left(D\right)$ at 0 ≤ apparent diffusion coefficient (ADC) ≤ 0.6 μm^2/ms. The summation of the remaining $f\left(D\right)$ at 0.6 < ADC ≤ 2 (for *ex vivo*) and 0.6 < ADC ≤ 3 (for *in vivo*) μm^2/ms represents non-restricted isotropic diffusion, which putatively denotes vasogenic edema and cerebrospinal fluid (20, 39–41).

Regions of interest (ROI) were manually drawn in the center of each optic nerve on the diffusion-weighted image, which corresponded to the diffusion gradient direction perpendicular to optic nerves, to minimize partial volume effects. ROIs were then transferred to the parametric maps to calculate the mean for each of the DBSI metrics.

ROI for DBSI-derived axon volume

Separate ROIs encompassing the whole optic nerve for axon volume calculation were drawn on the diffusion weighted images (DWI) orthogonal to the optic nerve, which were larger than the ROIs for DBSI metrics. The fiber fraction was measured of this larger ROI. DBSI-derived axon volume was calculated from the optic nerve volume (the entire ROIs on DWIs) multiplying by corresponding DBSI fiber fraction of this larger ROI.

Immunohistochemistry

Optic nerve pairs with chiasm were dissected (Supplementary Figure S2A) and embedded in 2% agar first (42). The agar block was embedded with liquid paraffin and the optic nerve was placed at the bottom of the embedding mold. The paraffin blocks were then sectioned from the optic chiasm at 20-μm thickness. Once passing the region of the optic chiasm, the sectioning thickness was reduced to 5-μm for 40 slices. The sectioning region reached the MRI imaging region (Supplementary Figure S2A, yellow rectangle), and the cross-sectional left and right optic nerves were shown as two circles (Supplementary Figure S2B, red arrows). The paraffin sectioning slices were deparaffinized and rehydrated for immunohistochemistry (IHC) analysis. Three nerves were damaged during the extraction process, and the other 41 nerves were used for paraffin embedding process. Sections were blocked with 5% normal goat serum and 1% bovine serum albumin in PBS for 30 min at room temperature to prevent non-specific binding. Slides were then incubated overnight at 4°C with primary antibody and then 1 h at room temperature with the appropriate secondary antibody. Primary antibodies used were anti-total neurofilament (SMI-312, staining both injured and intact axons, BioLegend, 1:300), anti-phosphorylated neurofilament (SMI-31, reflecting intact axons, BioLegend, 1:300), and anti-myelin basic protein (MBP, assessing myelin sheaths, Sigma, 1:300). Secondary antibodies were goat anti-mouse or goat anti-rabbit (Invitrogen, 1:240), which were conjugated to either Alexa 488 for SMI-31, SMI-312, or MBP. Slides were mounted with Vectashield Mounting Medium for DAPI (4′, 6-dianidino-2-phenylindole, detecting

cell nuclei, Vector Laboratory Inc., Burlingame, CA) and coverslipped. Images were acquired on a Nikon Eclipse 80i fluorescence microscope with MetaMorph software (Universal Imaging Corporation, Sunnyvale, CA) at 100× magnifications.

Histological data analysis

The whole field of SMI-31, MBP, and DAPI staining images at 100× magnification was captured with the same fluorescent light intensity and exposure time. All captured images were converted to 8-bit grayscale and analyzed using threshold, edge enhancement, analyze particles, and gray level watershed segmentation functions of ImageJ.[1]

1 http://bigwww.epfl.ch/sage/soft/watershed/

Statistical analysis

The correlations of histology and VA data with DBSI measurements were analyzed by a mixed random effect regression that accounted within mouse correlation between eye measurements. MRI measurements were taken from all eyes of sham and TBI mice. A mixed two-way ANOVA was performed between sham and TBI groups for comparing DBSI, DTI, and histology data. The correlation of histology data and DBSI measurements was analyzed by using Pearson Correlation Coefficients.

Results

Inconsistency between visual acuity and *in vivo* DBSI assessments

VA of TBI mice was unilaterally or bilaterally affected (Figure 1). At 1 day after TBI, VA was impaired in 3 out of 10 eyes and progressed

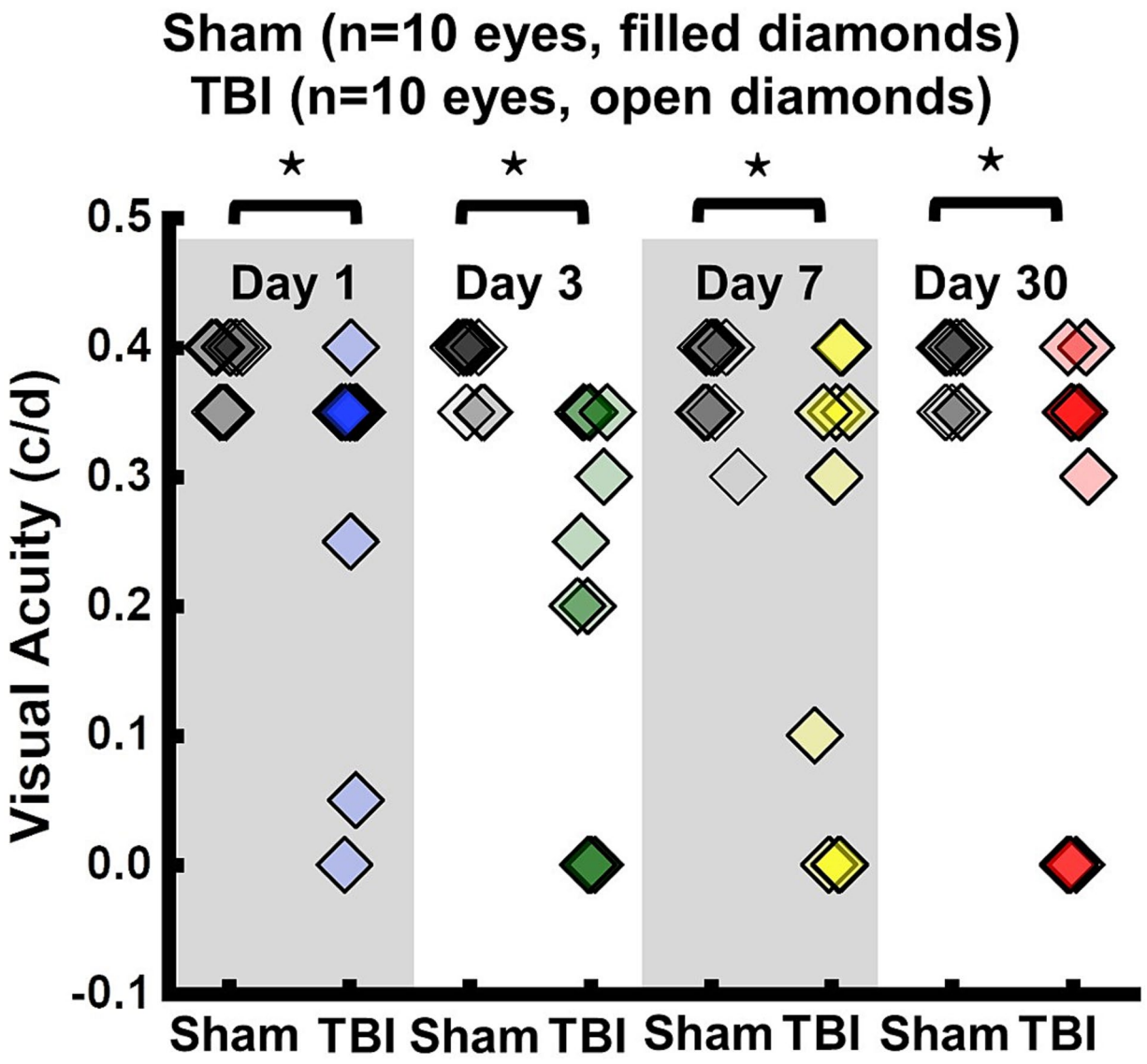

FIGURE 1
Longitudinal visual acuity (VA) of sham (filled diamonds) and TBI (open diamonds) eyes 1, 3, 7, and 30 days after TBI. VA was impaired in 3 out of 10 eyes, 9 out of 10 eyes, 4 out of 10 eyes, and 3 out of 10 eyes, at 1, 3, 7, and 30 days after TBI, respectively. ⋆ indicates $p < 0.05$.

to 9 out of 10 impaired eyes at 3 days after TBI. VA improved to impairment in 4 out of 10 and 3 out of 10 eyes at 7 and 30 days after TBI, respectively (Figure 1). DBSI metrics of optic nerves, however, were bilaterally affected with decreased DBSI-$\lambda_{||}$, elevated DBSI-$\lambda_{\perp}$, increased DBSI restricted (putative inflammatory cellularity) fraction, and decreased fiber fraction at 1, 3, 7, and 30 days after TBI (Table 1).

Representative DBSI metrics and VA from one sham mouse at 1, 3, 7, and 30 days after sham operation demonstrated that DBSI metrics describe normal nerve structure, consistent with normal VA (Figure 2). Comparing to sham optic nerves, the increased DBSI restricted fraction (Figures 3E–H), decreased fiber fraction (Figures 3I–L), and decreased DBSI-$\lambda_{||}$ in the representative TBI mouse optic nerves at 1, 3, 7, and 30 days after injury, suggesting increased cellularity, reduced axonal density, and axonal injury. The increased DBSI-$\lambda_{\perp}$ was shown at 3, 7, and 30 days after injury (Figures 3R–T), indicating myelin injury in the TBI optic nerves. In addition, the increased non-restricted fraction and optic nerve shrinkage were shown at 30 days after injury (Figures 3D,H,L,P,T), reflecting vasogenic edema and atrophy. Moreover, the volume of the optic nerve was 0.117 (left) and 0.151 (right) mm^3 vs. 0.148 (left) and 0.172 (right) mm^3 at 1 and 3 days after injury, respectively, while the fiber fraction remained unchanged (Figures 3I,J), suggesting cytotoxic edema of the optic nerves at the acute stage after TBI. The corresponding VA in TBI was inconsistent with optic nerve pathologies (Figure 3).

TABLE 1 Quantitative longitudinal DBSI/DTI results of sham and TBI optic nerves.

In vivo		Day 1	Day 3	Day 7	Day 30
DBSI non-restricted fraction	Sham	0.03 ± 0.043	0.05 ± 0.043	0.06 ± 0.035	0.06 ± 0.054
	TBI	0.03 ± 0.029	0.05 ± 0.025	0.07 ± 0.054	0.10 ± 0.048
DBSI restricted fraction	Sham	0.03 ± 0.014	0.03 ± 0.018	0.04 ± 0.036	0.05 ± 0.014
	TBI	0.12 ± 0.050*	0.11 ± 0.046*	0.12 ± 0.056*	0.18 ± 0.069*
DBSI-derived Axon Volume (mm^3)	Sham	0.11 ± 0.009	0.10 ± 0.006	0.11 ± 0.009	0.11 ± 0.007
	TBI	0.10 ± 0.009	0.11 ± 0.009*	0.09 ± 0.014*	0.08 ± 0.022*
DBSI $\lambda_{||}$ (μm^2/ms)	Sham	1.89 ± 0.128	1.89 ± 0.092	1.84 ± 0.088	1.84 ± 0.210
	TBI	1.47 ± 0.178*	1.59 ± 0.163*	1.55 ± 0.161*	1.61 ± 0.211*
DBSI $\lambda_{\perp}$ (μm^2/ms)	Sham	0.15 ± 0.038	0.17 ± 0.056	0.15 ± 0.039	0.14 ± 0.024
	TBI	0.18 ± 0.029	0.22 ± 0.041*	0.21 ± 0.044*	0.23 ± 0.053*
DTI $\lambda_{||}$ (μm^2/ms)	Sham	1.72 ± 0.124	1.75 ± 0.058	1.68 ± 0.066	1.62 ± 0.183
	TBI	1.19 ± 0.229*	1.21 ± 0.220*	1.20 ± 0.199*	1.07 ± 0.184*
DTI $\lambda_{\perp}$ (μm^2/ms)	Sham	0.17 ± 0.046	0.20 ± 0.051	0.19 ± 0.040	0.20 ± 0.058
	TBI	0.20 ± 0.025	0.26 ± 0.039*	0.28 ± 0.046*	0.34 ± 0.060*
DTI FA	Sham	0.88 ± 0.040	0.86 ± 0.039	0.87 ± 0.032	0.85 ± 0.062
	TBI	0.81 ± 0.042*	0.75± 0.059*	0.71 ± 0.089*	0.61 ± 0.0117*
DTI MD (μm^2/ms)	Sham	0.23 ± 0.012	0.24 ± 0.008	0.23 ± 0.009	0.22 ± 0.015
	TBI	0.18 ± 0.027*	0.19± 0.024*	0.20 ± 0.019*	0.19 ± 0.013*

*indicates $p < 0.05$.

In vivo DBSI metrics reflected coexisting pathologies in the TON optic nerve

DBSI metrics could reflect coexisting pathologies in the optic nerve of TBI mice during the observation period up to 30 days after TBI. Comparing to sham mice, the DBSI non-restricted fraction (putative biomarker of vasogenic edema) was not significantly different from 1, 3, 7, and 30 days after TBI (Figure 4A; Table 1). DBSI restricted fraction (Figure 4B; Table 1) elevated, compared to sham mice, by 300% (0.12 ± 0.050 vs. 0.03 ± 0.014, TBI vs. sham, $p < 0.05$), 267% (0.11 ± 0.046 vs. 0.03 ± 0.018, TBI vs. sham, $p < 0.05$), 200% (0.12 ± 0.056 vs. 0.04 ± 0.036, TBI vs. sham, $p < 0.05$), and 260% (0.18 ± 0.069 vs. 0.05 ± 0.014, TBI vs. sham, $p < 0.05$) at 1, 3, 7, and 30 days, respectively, after TBI. DBSI-$\lambda_{||}$ (Figure 4C; Table 1) decreased by 22% (1.89 ± 0.128 vs. 1.47 ± 0.178 μm^2/ms, Sham vs. TBI, $p < 0.05$), 16% (1.89 ± 0.092 vs. 1.59 ± 0.638 μm^2/ms, Sham vs. TBI, $p < 0.05$), 15% (1.84 ± 0.088 vs. 1.55 ± 0.161 μm^2/ms, Sham vs. TBI, $p < 0.05$), and 13% (1.84 ± 0.210 vs. 1.61 ± 0.211 μm^2/ms, Sham vs. TBI, $p < 0.05$) at 1, 3, 7, and 30 days, respectively, after TBI. DBSI-$\lambda_{\perp}$ (Figure 4D; Table 1) increased by 16% (0.15 ± 0.038 vs. 0.18 ± 0.029 μm^2/ms, Sham vs. TBI, $p = 0.13$), 30% (0.17 ± 0.056 vs. 0.22 ± 0.041 μm^2/ms, Sham vs. TBI, $p < 0.05$), 29% (0.15 ± 0.039 vs. 0.21 ± 0.044 μm^2/ms, Sham vs. TBI, $p < 0.05$), and 34% (0.14 ± 0.024 vs. 0.23 ± 0.053 μm^2/ms, Sham vs. TBI, $p < 0.05$) at 1, 3, 7, and 30 days, respectively, after TBI.

In vivo DTI metrics were confounded by coexisting pathologies in the TON optic nerve

In contrast to DBSI metrics, DTI-$\lambda_{||}$ (Figure 4E; Table 1) and DTI-$\lambda_{\perp}$ (Figure 4F; Table 1) showed an exaggerated decrease and increase, respectively, suggesting DTI-derived axonal injury and myelin injury were confounded by inflammation and axonal loss. Comparing to the sham mouse optic nerve, reduced DTI fractional anisotropy (FA; Figure 4G; Table 1) and DTI mean diffusivity (MD, Figure 4H; Table 1) reflected the combined effects of axonal injury, inflammation, and axonal loss.

In vivo DBSI detected axonal loss in the TON optic nerve

DBSI-derived fiber fraction may reflect apparent fiber (i.e., axon) density that is confounded by dilution effects from other pathological components. DBSI-derived fiber fraction decreased by 7% (0.81 ± 0.060 vs. 0.76 ± 0.038, Sham vs. TBI, $p < 0.05$), 1% (0.77 ± 0.031 vs. 0.76 ± 0.024, Sham vs. TBI, $p = 0.29$), 6% (0.76 ± 0.044 vs. 0.72 ± 0.065, Sham vs. TBI, $p = 0.10$), and 20% (0.81 ± 0.082 vs. 0.61 ± 0.107, Sham vs. TBI, $p < 0.05$) at 1, 3, 7, and 30 days, respectively, after TBI. To quantify the extent of axons, a quantitative metric was developed to remove the dilution effects resulting from vasogenic edema and other complications. The metric was developed by multiplying DBSI anisotropic fiber fraction with optic nerve volume (assessed by conventional or diffusion-weighted MRI) resulting in a metric reflecting axon content with, i.e., *axon (fiber) volume* (Figure 5A). The nerve volume assessed using diffusion-weighted images with DW direction perpendicular to the fiber tract changed 4% (0.13 ± 0.011 vs. 0.14 ± 0.011 mm3, Sham vs. TBI, $p = 0.03$), 12% (0.13 ± 0.006 vs. 0.15 ± 0.011 mm3, Sham vs. TBI, $p < 0.05$), −17% (0.15 ± 0.011 vs. 0.12 ± 0.017 mm3, Sham vs. TBI, $p < 0.05$), and −15%

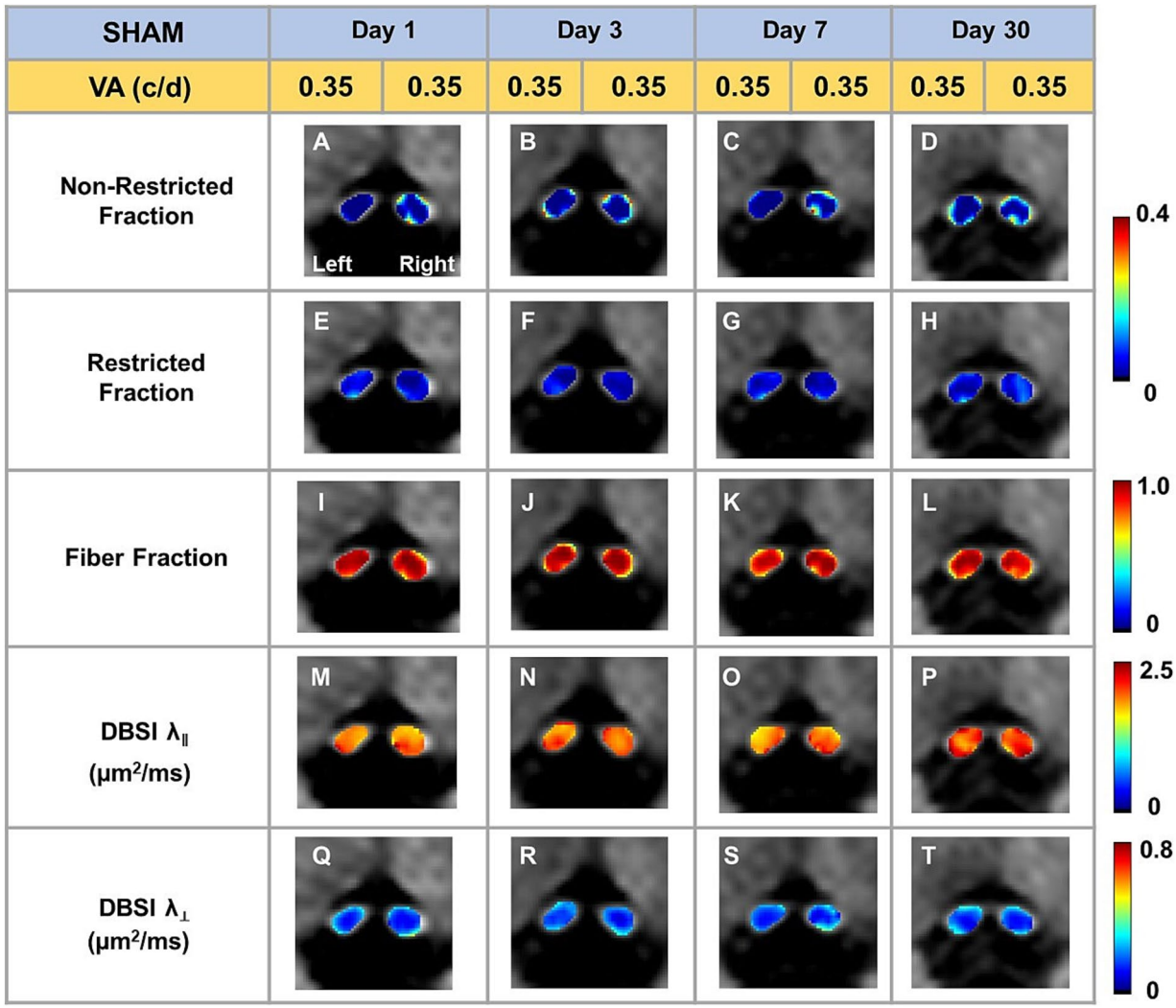

FIGURE 2
Representative DBSI metrics were overlaid on gray-scale diffusion-weighted images of sham optic nerves. DBSI non-restricted fraction **(A–D)**, restricted fraction **(E–H)**, Fiber fraction **(I–L)**, DBSI axial diffusivity ($\lambda_{\parallel}$) **(M–P)**, and DBSI radial diffusivity ($\lambda_{\perp}$) **(Q–T)** were consistent at, 1, 3, 7, and 30 days after TBI. The corresponding VA was at the normal score all the time.

(0.14 ± 0.018 vs. 0.12 ± 0.016 mm3, Sham vs. TBI, $p < 0.05$) at 1, 3, 7, and 30 days, respectively, after TBI (Table 1). DBSI-derived axon volume decreased 2% (0.11 ± 0.009 vs. 0.10 ± 0.009 mm^3, Sham vs. TBI, $p = 0.58$), −10% (0.10 ± 0.006 vs. 0.11 ± 0.009 mm^3, Sham vs. TBI, $p < 0.05$), 21% (0.11 ± 0.009 vs. 0.09 ± 0.014 mm^3, Sham vs. TBI, $p < 0.05$), and 30% (0.11 ± 0.007 vs. 0.08 ± 0.022 mm^3, Sham vs. TBI, $p < 0.05$) at 1, 3, 7, and 30 days, respectively, after TBI (Figure 5B; Table 1).

Optic nerve axonal injury at 3 days after TBI (*ex vivo* cohort)

DBSI non-restricted fraction was not significant differences between the sham and TBI group (Table 2). DBSI restricted fraction (Table 2) was elevated, compared to sham mice, by 47% (0.19 ± 0.055 vs. 0.10 ± 0.055, TBI vs. sham, $p < 0.05$). DBSI-$\lambda_{\parallel}$ (Table 2) decreased by 28% (0.74 ± 0.090 vs. 0.53 ± 0.070 μm^2/ms, Sham vs. TBI, $p < 0.05$). DBSI-$\lambda_{\perp}$ (Table 2) increased by 50% (0.06 ± 0.026 vs. 0.09 ± 0.017 μm^2/ms, Sham vs. TBI, $p < 0.05$). DBSI fiber fraction decreased by 9% (0.68 ± 0.050 vs. 0.62 ± 0.096 μm^2/ms, Sham vs. TBI, $p = 0.06$). The nerve volume assessed using diffusion-weighted images with DW direction perpendicular to the fiber tract changed by 10% (0.10 ± 0.012 vs. 0.09 ± 0.018 mm^3, Sham vs. TBI, $p = 0.13$). DBSI-derived axon volume (Table 2) exhibited a 14% decrease (0.07 ± 0.009 vs. 0.06 ± 0.015 mm^3, Sham vs. TBI, $p < 0.05$). Comparing DBSI metrics, DTI-$\lambda_{\parallel}$ (Table 2) and DTI-$\lambda_{\perp}$ (Table 2) showed an exaggerated decrease and increase, respectively. Comparing to the sham mouse optic nerve, reduced DTI-FA (Table 2) and DTI-MD (Table 2) were observed.

Representative IHC results revealed axonal loss (reduced SMI-312 area; Figures 6A,E), demyelination (reduced MBP area fraction; Figures 6B,F), severe axonal swelling (Figures 6E–G, white arrows), axonal injury (reduced SMI-31 density; Figures 6B,C,G)

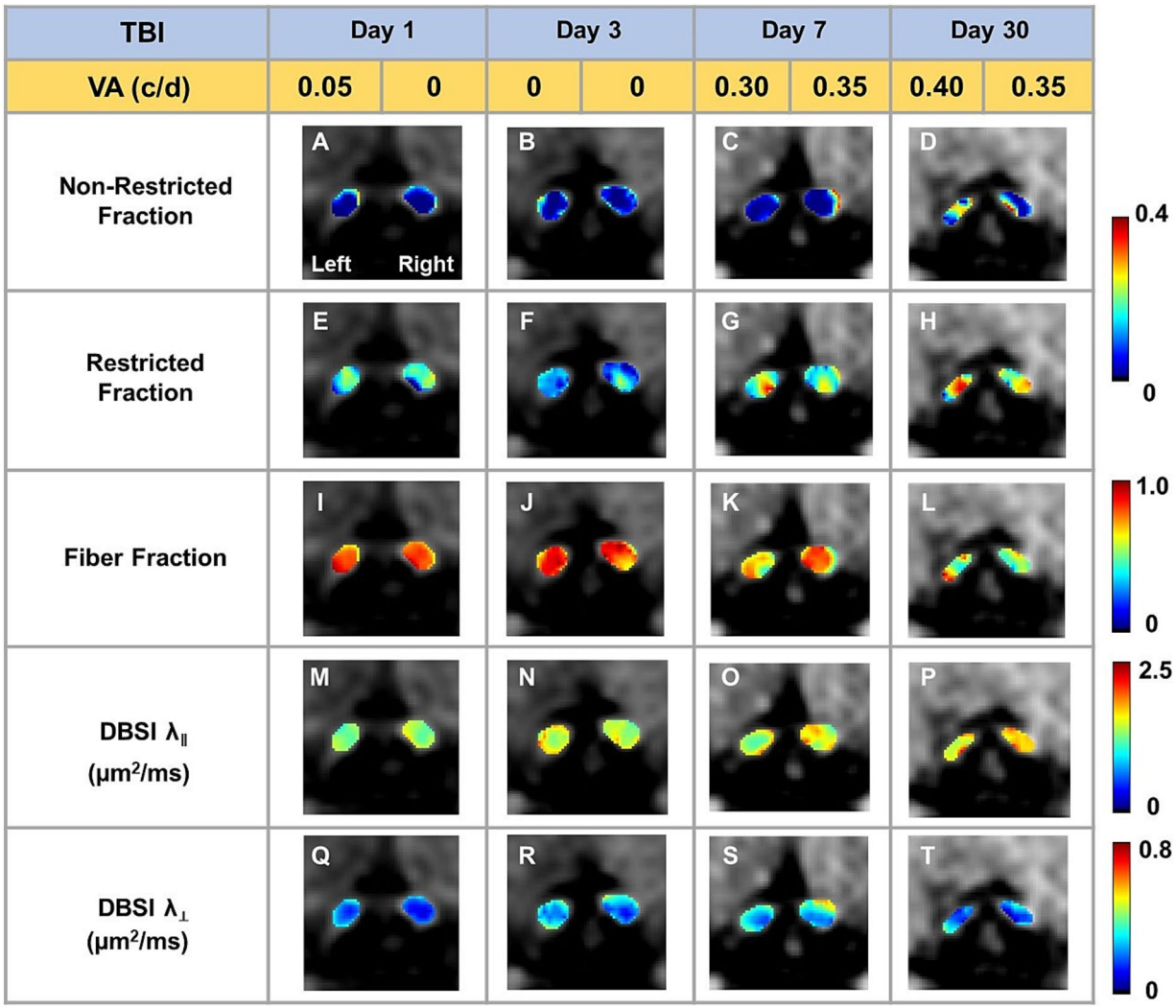

FIGURE 3
Representative DBSI metrics were overlaid on gray-scale diffusion-weighted images of TBI optic nerves. Compared to sham optic nerves in Figure 2, elevated DBSI restricted fraction **(E–H)**, reduced fiber fraction **(I–L)**, reduced DBSI axial diffusivity ($\lambda_{\parallel}$) **(M–P)**, and increased DBSI radial diffusivity ($\lambda_{\perp}$) **(Q–T)** were shown at 1, 3, 7, and 30 days after TBI. The corresponding VA was not consistent with DBSI metrics.

and increased cellularity (increased DAPI density; Figures 6D,H) in the optic nerves of the TBI mice. The correlations of DBSI-derived axon volume (Figure 6I, $r^2 = 0.4918$, $p = 0.0002$), DBSI $\lambda_{\perp}$ (Figure 6J, $r^2 = 0.4393$, $p = 0.0006$), DBSI $\lambda_{\parallel}$ (Figure 6K, $r^2 = 0.4641$, $p = 0.0003$), and DBSI restricted fraction (Figure 6L, $r^2 = 0.4823$, $p = 0.0002$) were consistent with SMI-312 area, MBP area fraction, SMI-31 density, and DAPI density, suggesting that DBSI biomarkers reflect coexisting pathologies of the optic nerves in the TBI mice. The reduced SMI-312 area (0.064 ± 0.013 vs. 0.045 ± 0.001 mm^2, Sham vs. TBI, $p < 0.05$; Table 3), and MBP area fraction (0.25 ± 0.03 vs. 0.18 ± 0.05, Sham vs. TBI, $p < 0.05$; Table 3), SMI-31 density ($189{,}969 \pm 24{,}492$ vs. $108{,}139 \pm 42{,}917$ #/mm^2, Sham vs. TBI, $p < 0.05$; Table 3) in the TBI group suggested axonal loss, demyelination, and axonal injury in their optic nerves. The increased DAPI density (690 ± 109 vs. 864 ± 129 #/mm^2, Sham vs. TBI, $p < 0.05$; Table 3) in the TBI group suggested area increased cellularity in the TBI optic nerves.

IHC of optic nerves at the end of longitudinal MRI

Representative IHC of optic nerves revealed axonal loss (reduced SMI-312 intensity; Figures 7A,E), myelin injury (reduced MBP area fraction; Figures 7B,F), axonal injury (reduced SMI-31 density; Figures 7C,G), and increased cellularity (increased DAPI density; Figures 7D,H) in the optic nerves of TBI mice. The correlations of DBSI-derived axon volume (Figure 7I, $r^2 = 0.661$, $p = 0.0026$), DBSI $\lambda_{\perp}$ (Figure 7J, $r^2 = 0.3456$, $p = 0.07$), DBSI $\lambda_{\parallel}$ (Figure 7K, $r^2 = 0.7065$, $p = 0.0023$), and DBSI restricted fraction (Figure 7L, $r^2 = 0.5841$, $p = 0.01$) was consistent with SMI-312 area, MBP intensity, SMI-31 density, and DAPI density, suggesting that DBSI reflected coexisting pathologies in the optic nerves of TBI mice. The reduced SMI-312 area (0.088 ± 0.015 vs. 0.053 ± 0.007 mm^2, Sham vs. TBI, $p < 0.05$; Table 4), MBP area fraction (0.27 ± 0.04 vs. 0.20 ± 0.05, Sham vs. TBI, $p < 0.05$; Table 4), SMI-31 density ($125{,}197 \pm 37{,}281$ vs. $74{,}336 \pm 42{,}548$ #/mm^2,

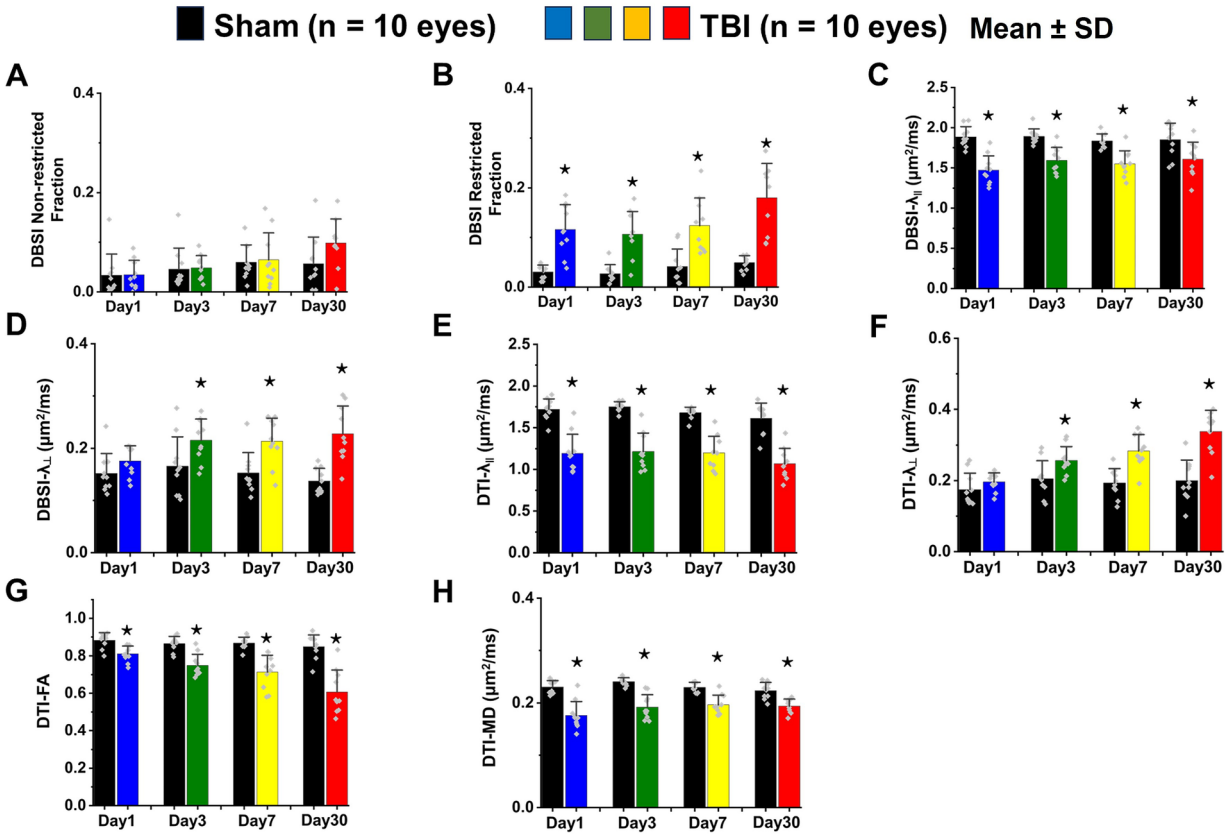

FIGURE 4
Bar graphs of DBSI **(A–D)** and DTI **(E–H)** metrics. * indicates $p < 0.05$.

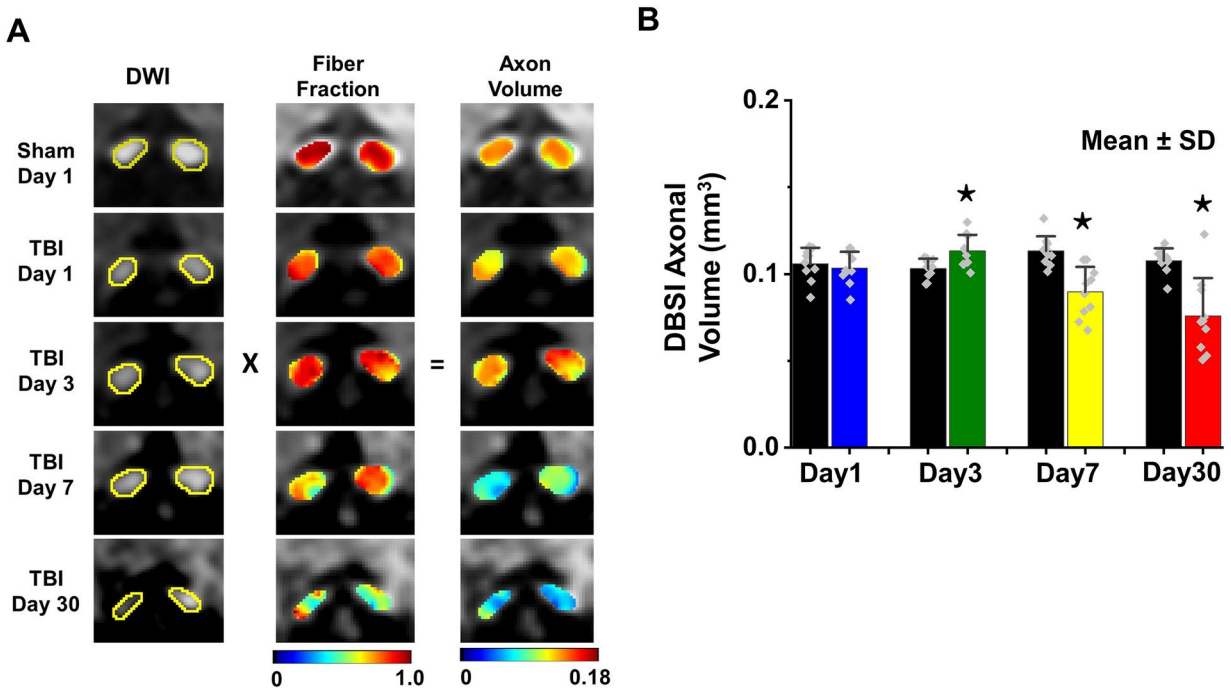

FIGURE 5
DBSI-axonal volume (unit in mm^3) was derived by multiplying nerve volume (unit in mm^3) with fiber fraction **(A)**. DBSI-derived axonal volume of sham and TBI optic nerves from 1, 3, 7, and 30 **(B)**. * indicates $p < 0.05$.

Sham vs. TBI, $p < 0.05$; Table 4) in the TBI group suggested axonal loss, demyelination, and axonal injury in the TBI optic nerves. The increased DAPI density (479 ± 92 vs. 745 ± 133 #/mm^2, Sham vs. TBI, $p < 0.05$; Table 4) in the TBI group suggested increased cellularity in the TBI optic nerves.

TABLE 2 Quantitative DBSI/DTI results of sham and TBI optic nerves at Day 3 (*ex vivo* cohort).

Ex vivo		Day 3
DBSI non-restricted fraction	Sham	0.06 ± 0.026
	TBI	0.07 ± 0.058
DBSI restricted fraction	Sham	0.10 ± 0.042
	TBI	0.19 ± 0.055*
DBSI-derived axon volume (mm^3)	Sham	0.07 ± 0.009
	TBI	0.06 ± 0.015*
DBSI $\lambda_{\parallel}$ (μm^2/ms)	Sham	0.74 ± 0.090
	TBI	0.53 ± 0.070*
DBSI $\lambda_{\perp}$ (μm^2/ms)	Sham	0.06 ± 0.026
	TBI	0.09 ± 0.017*
DTI $\lambda_{\parallel}$ (μm^2/ms)	Sham	0.61 ± 0.090
	TBI	0.42 ± 0.075*
DTI $\lambda_{\perp}$ (μm^2/ms)	Sham	0.08 ± 0.071
	TBI	0.12 ± 0.036*
DTI FA	Sham	0.85 ± 0.071
	TBI	0.68 ± 0.102*
DTI MD (μm^2/ms)	Sham	0.09 ± 0.015
	TBI	0.07 ± 0.013*

*indicates $p < 0.05$.

Discussion

In the current study, longitudinal DBSI and VA assessments were performed to investigate optic nerve pathology at 1, 3, 7, and 30 days after TBI. The results suggested that DBSI detected axonal injury, myelin damage, axonal loss, and inflammatory cellularity in the optic nerves of mice with TBI. The axonal loss identified in this study indicates that axonal volume is a valid marker of axonal extent. This study shows that optic nerve changes induced by TBI can be reproduced in the modCHIMERA TBI mice.

To evaluate the indirect TON, VA examinations were performed. Previously, it was identified that VA was sensitive to identify the onset of acute optic neuritis in myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE) mice (26, 28, 34, 35). In the current study, VA of TBI mice was unilaterally or bilaterally affected (Figure 1), but coexisting pathologies were detected in both optic nerves (Figure 3; Table 1). The current data indicated that VA does not reflect the optic nerve pathology of indirect TON in modCHIMERA mice. VA impairment in these mice may be confounded by psychophysical deficits in the modCHIMERA model as suggested by previously reported social and motor deficits (32), although the motor deficits are short lived.

Optic neuritis is one of the prominent and early pathologies of EAE mice (43). In acute EAE mice, change in VA was consistent with optic nerve pathology before chronic neurological deficits interfered with the optomotor reflex assessment (26, 34, 35). In indirect TON, a

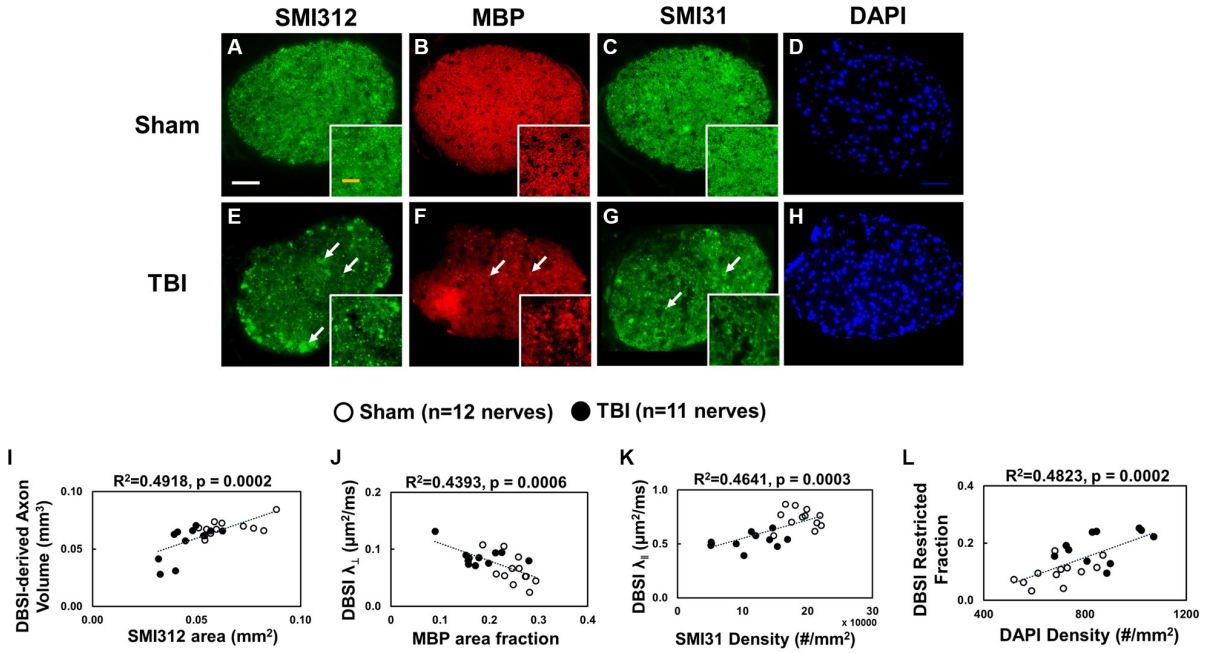

FIGURE 6
Representative 100× IHC from one sham **(A–D)** and one TBI **(E–H)** optic nerve (tissues were processed after *ex vivo* DBSI, 3 days after impact). The correlation of SMI-312 area, MBP area fraction, SMI-31 and DAPI density with DBSI-derived axon volume **(I)**, DBSI $\lambda_{\perp}$ **(J)**, DBSI $\lambda_{\parallel}$ **(K)**, and DBSI restricted isotropic fraction **(L)** suggested that DBSI was able to reflect the severity of axonal loss, myelination, axonal integrity, and inflammatory-increased cellularity, respectively. White scale bar: 50 μm; Yellow scale bar: 25 μm.

compensatory mechanism might play a role in the normalization of VA in the chronic stage (44). Therefore, VA may not be sensitive enough for visual function evaluation in indirect TON of TBI mouse models. For a more accurate assessment of visual function in indirect TON, behavioral independent assessments would improve the analyses.

Optic nerve pathologies in indirect TON include cytotoxic edema, vasogenic edema, and inflammation with activated microglia and macrophages (45, 46), followed by Wallerian degeneration (47, 48). Decreased apparent diffusion coefficient has been shown to associate with optic nerve injury and to be used as a surrogate marker of sight loss in unconscious patients (49). The decreased axial and mean diffusivity, believed to reflect damage of the axolemma and axonal swelling, has been proposed to serve as a biomarker of axonal damage and as a predictor of initial visual acuity and potential visual recovery in patients with TON (6). The current findings in TBI mice are consistent with TON patients exhibiting decreased DTI and DBSI derived axial diffusivity although the decreased axial diffusivity was seen in optic nerves of normal and impaired visual acuity in TBI mice.

TABLE 3 Quantitative IHC results of sham and TBI optic nerves at Day 3 (*ex vivo* cohort).

Ex vivo	SMI312 (mm^2)	MBP fraction	SMI31 (#/mm^2)	DAPI (#/mm^2)
Sham	0.064 ± 0.013	0.25 ± 0.03	189,969 ± 24,492	690 ± 109
TBI	0.045 ± 0.001*	0.18 ± 0.05*	108,139 ± 42,917*	864 ± 129*

*indicates $p < 0.05$.

The results suggest the presence of subclinical optic nerve pathologies that may escape timely detection and treatment in TON.

A previous study has identified that DBSI derived axon volume detected axonal loss in the presence of white matter tract swelling (26). Another marker of axonal swelling is decreased radial diffusivity, as a result of axonal crowding (6). The clinical correlation of nerve swelling is questionable and seems unpredictable. Stahl et al. presented a 21-year-old male patient with right-sided visual loss after sustaining a penetrating orbital trauma, with minimal ocular trauma, from a metal rod (49). The MRI showed a unilateral reduction of the subarachnoid space of the optic nerve on the affected side, with a normal optic nerve diameter. The patient had permanent visual loss. Becker et al. presented a case whereby a patient suffered from a skull base fracture and had axonal injury of the optic nerve (21). DWI showed widening of the left optic nerve at the level of the orbital apex. This patient also had permanent visual loss.

DBSI quantitatively assesses axonal volume that is capable of quantifying the cytotoxic edema induced axonal swelling without being confounded by extra-fiber swelling resulting from inflammatory cell infiltration and vasogenic edema (assessed by non-restricted diffusion). This has been consistent with our previous study showing DBSI quantified axonal loss in the presence of nerve swelling in acute spinal cord injury (31). Thus, DBSI complements the conventional MRI measured cross-sectional areas of optic nerves and spinal cords by quantitatively distinguishing and assessing intra- and extra-fiber swelling.

In this study, it was identified that significantly increased nerve volume can be attributed to increased DBSI restricted fraction (extra-axonal swelling), increased DBSI axon volume

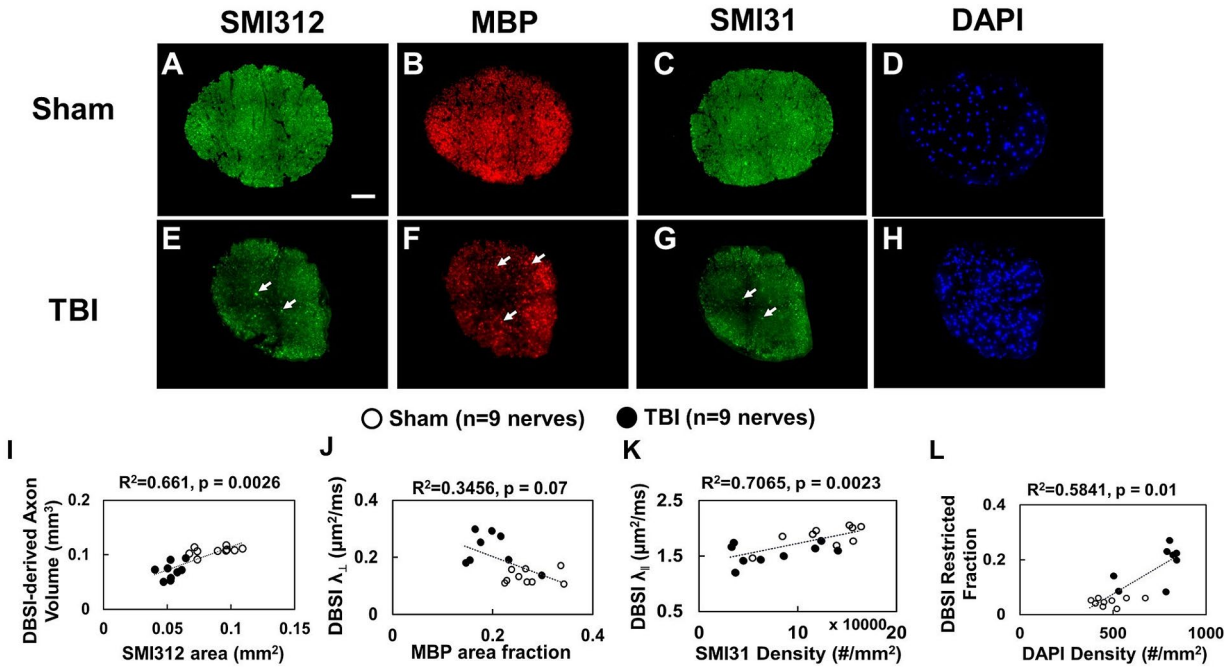

FIGURE 7
Representative 100× IHC from one sham **(A–D)** and one TBI **(E–H)** optic nerve (tissues were saved right after *in vivo* DBSI, 30 days after impact). The correlation of SMI-312 area, MBP area fraction, SMI-31 and DAPI density with DBSI-derived axon volume **(I)**, DBSI $\lambda_{\perp}$ **(J)**, DBSI $\lambda_{\parallel}$ **(K)**, and DBSI restricted isotropic fraction **(L)** suggested that DBSI was able to reflect the severity of axonal loss, myelination, axonal integrity, and inflammatory-increased cellularity, respectively. White scale bar: 50 μm.

TABLE 4 Quantitative IHC results of sham and TBI optic nerves at Day 30 (*in vivo* cohort).

In vivo	SMI312 (mm^2)	MBP fraction	SMI31 (#/mm^2)	DAPI (#/mm^2)
Sham	0.088 ± 0.015	0.27 ± 0.04	125,197 ± 37,281	479 ± 92
TBI	0.053 ± 0.007*	0.20 ± 0.05*	74,336 ± 42,548*	745 ± 133*

*indicates $p < 0.05$.

(intra-axonal swelling), unchanged DBSI fiber fraction (axonal density), and unchanged DBSI non-restricted fraction (extra-axonal swelling, i.e., vasogenic edema) at 3 days after TBI. For the *in vivo* cohort, the acute nerve swelling can be partially attributed to the axonal swelling (i.e., cytotoxic edema) as reflected by the increased DBSI-derived axonal volume at 3 days after TBI. To further investigate the cytotoxic-edema impact of DBSI-derived axonal volume at 3 days after TBI, the *ex vivo* cohort was used to validate the correlation between DBSI and histology (Figure 7; Table 2) since histological fixation typically dehydrates and shrinks the processed tissue, masking vasogenic edema induced tissue swelling (50). The *ex vivo* brain samples underwent 24-h 4% PFA fixation, then transferred to the PBS solution prior to the DBSI scan. The *ex vivo* nerve volume at 3 days after TBI was examined for detecting cytotoxic edema with minimized contribution of vasogenic edema. DBSI-derived axonal volume at 3 days after TBI detected axonal loss consistent with the histological results (Figure 7).

Although DTI metrics may not reflect the true axonal and myelin pathologies due to confounds from coexisting pathologies such as inflammatory cell infiltration and vasogenic edema as previously reported (22–25). Current longitudinal diffusion-weighted MRI examination of optic nerves in mice revealed the same trend of both DTI and DBSI derived axial ($\lambda_{||}$, decreased comparing with that of sham) and radial ($\lambda_{\perp}$, increased comparing with that of sham) diffusivity in TBI mice, suggesting axonal and myelin injury. This is consistent with a previously reported retrospective investigation on the diffusion-weighted MRI signal intensity of the optic nerve in 29 patients with TON (51), where a hyperintense signal was seen in injured eyes. The current study revealed an increased DTI $\lambda_{\perp}$ and DBSI $\lambda_{\perp}$ from days 1 to 30 after TBI, suggesting myelin injury. This is consistent with the reduced MBP area fraction at 3 and 30 days after TBI. A similar extent of myelin injury was identified by Qiu et al., who examined NF-1 and MBP in a repetitive mild TBI mouse model 7-months after injury and found significantly reduced expression of both proteins when compared with sham animals (52). Khan et al. reported similar observations in their repetitive TBI mice model (53).

Although the current study did not examine the retinal pathology or a specific mechanism of TON along the entire optic nerve tract, the localized findings are encouraging and validate the utility of DBSI to detect and distinguish optic nerve injury types and components. The results demonstrated the presence of TON in modCHIMERA-induced TBI mice. Future studies may consider exploring the intersegmental changes of the optic nerve in a TBI animal model (6, 51) and variations in injury patterns using DBSI and resting state functional imaging (54, 55). The results from the current study should be interpreted under the context of the limitations of modCHIMERA-induced TBI in mice (32). This study may serve as a catalyst to encourage bench-to-bedside efforts to detect TON using a novel imaging modality and potentially reduce the burden of TON in patients with TBI.

Conclusion

DBSI and DTI suggested subclinical injury of indirect TON in TBI mice. However, DTI-derived metrics are confounded by coexisting pathologies, lacking the needed accuracy or specificity in detecting optic nerve injuries. DBSI is capable of detecting and distinguishing coexisting optic nerve pathologies. DBSI is potentially more effective for detecting the clinically silent optic nerve pathologies in indirect TON. Thus, DBSI may serve as an outcome measure of TON.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by Washington University Institutional Animal Care and Use Committee. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

H-CY: Data curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. RL: Data curation, Validation, Writing – original draft, Writing – review & editing. AS: Data curation, Methodology, Writing – review & editing. MW: Data curation, Methodology, Writing – review & editing. TK: Writing – review & editing. S-KS: Conceptualization, Validation, Writing – original draft, Writing – review & editing, Funding acquisition. T-HL: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1269817/full#supplementary-material

References

1. Goodrich GL, Flyg HM, Kirby JE, Chang CY, Martinsen GL. Mechanisms of TBI and visual consequences in military and veteran populations. *Optom Vis Sci*. (2013) 90:105–12. doi: 10.1097/OPX.0b013e31827f15a1

2. Goodrich GL, Kirby J, Cockerham G, Ingalla SP, Lew HL. Visual function in patients of a polytrauma rehabilitation center: a descriptive study. *J Rehabil Res Dev*. (2007) 44:929–36. doi: 10.1682/JRRD.2007.01.0003

3. Chen YJ, Liang CM, Tai MC, Chang YH, Lin TY, Chung CH, et al. Longitudinal relationship between traumatic brain injury and the risk of incident optic neuropathy: a 10-year follow-up nationally representative Taiwan survey. *Oncotarget*. (2017) 8:86924–33. doi: 10.18632/oncotarget.21008

4. Houston KE, Paschalis EI, Angueira DC, Bronstad PM, Barrett AM, Iaccarino MA. Restoration of vision after brain injury using magnet glasses. *Am J Phys Med Rehabil*. (2017) 96:e70–4. doi: 10.1097/PHM.0000000000000592

5. Chen B, Zhang H, Zhai Q, Li H, Wang C, Wang Y. Traumatic optic neuropathy: a review of current studies. *Neurosurg Rev*. (2022) 45:1895–913. doi: 10.1007/s10143-021-01717-9

6. Bodanapally UK, Kathirkamanathan S, Geraymovych E, Mirvis SE, Choi AY, McMillan AB, et al. Diagnosis of traumatic optic neuropathy: application of diffusion tensor magnetic resonance imaging. *J Neuroophthalmol*. (2013) 33:128–33. doi: 10.1097/WNO.0b013e3182842553

7. Walsh FBPathological-Clinical Correlations. I. Indirect trauma to the optic nerves and chiasm. II. Certain cerebral involvements associated with defective blood supply. *Investig Ophthalmol*. (1966) 5:433–49.

8. Mohan K, Kecova H, Hernandez-Merino E, Kardon RH, Harper MM. Retinal ganglion cell damage in an experimental rodent model of blast-mediated traumatic brain injury. *Invest Ophthalmol Vis Sci*. (2013) 54:3440–50. doi: 10.1167/iovs.12-11522

9. Tzekov R, Quezada A, Gautier M, Biggins D, Frances C, Mouzon B, et al. Repetitive mild traumatic brain injury causes optic nerve and retinal damage in a mouse model. *J Neuropathol Exp Neurol*. (2014) 73:345–61. doi: 10.1097/NEN.0000000000000059

10. Tyler CW, Likova LT. Brain trauma impacts retinal processing: photoreceptor pathway interactions in traumatic light sensitivity. *Doc Ophthalmol*. (2022) 144:179–90. doi: 10.1007/s10633-022-09871-1

11. Kumaran AM, Sundar G, Chye LT. Traumatic optic neuropathy: a review. *Craniomaxillofac Trauma Reconstr*. (2015) 8:31–41. doi: 10.1055/s-0034-1393734

12. Yu-Wai-Man P. Traumatic optic neuropathy-clinical features and management issues. *Taiwan J Ophthalmol*. (2015) 5:3–8. doi: 10.1016/j.tjo.2015.01.003

13. Burke EG, Cansler SM, Evanson NK. Indirect traumatic optic neuropathy: modeling optic nerve injury in the context of closed head trauma. *Neural Regen Res*. (2019) 14:593–4. doi: 10.4103/1673-5374.247463

14. Li Y, Singman E, McCulley T, Wu C, Daphalapurkar N. The biomechanics of indirect traumatic optic neuropathy using a computational head model with a Biofidelic orbit. *Front Neurol*. (2020) 11:346. doi: 10.3389/fneur.2020.00346

15. Chalela JA. Traumatic optic neuropathy: the forgotten concussion. *Mil Med*. (2023) 188:398–400. doi: 10.1093/milmed/usac060

16. Singman EL, Daphalapurkar N, White H, Nguyen TD, Panghat L, Chang J, et al. Indirect traumatic optic neuropathy. *Mil Med Res*. (2016) 3:2. doi: 10.1186/s40779-016-0069-2

17. Klimo KR, Stern-Green EA, Shelton E, Day E, Jordan L, Robich M, et al. Structure and function of retinal ganglion cells in subjects with a history of repeated traumatic brain injury. *Front Neurol*. (2022) 13:963587. doi: 10.3389/fneur.2022.963587

18. Minakaran N, de Carvalho ER, Petzold A, Wong SH. Optical coherence tomography (OCT) in neuro-ophthalmology. *Eye*. (2021) 35:17–32. doi: 10.1038/s41433-020-01288-x

19. Gala F. Magnetic resonance imaging of optic nerve. *Indian J Radiol Imaging*. (2015) 25:421–38. doi: 10.4103/0971-3026.169462

20. Wang Y, Wang Q, Haldar JP, Yeh FC, Xie M, Sun P, et al. Quantification of increased cellularity during inflammatory demyelination. *Brain*. (2011) 134:3590–601. doi: 10.1093/brain/awr307

21. Becker M, Masterson K, Delavelle J, Viallon M, Vargas MI, Becker CD. Imaging of the optic nerve. *Eur J Radiol*. (2010) 74:299–313. doi: 10.1016/j.ejrad.2009.09.029

22. Kuroiwa T, Nagaoka T, Ueki M, Yamada I, Miyasaka N, Akimoto H, et al. Correlations between the apparent diffusion coefficient, water content, and ultrastructure after induction of vasogenic brain edema in cats. *J Neurosurg*. (1999) 90:499–503. doi: 10.3171/jns.1999.90.3.0499

23. Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y. Free water elimination and mapping from diffusion MRI. *Magn Reson Med*. (2009) 62:717–30. doi: 10.1002/mrm.22055

24. Naismith RT, Xu J, Tutlam NT, Scully PT, Trinkaus K, Snyder AZ, et al. Increased diffusivity in acute multiple sclerosis lesions predicts risk of black hole. *Neurology*. (2010) 74:1694–701. doi: 10.1212/WNL.0b013e3181e042c4

25. Anderson AW, Xie J, Pizzonia J, Bronen RA, Spencer DD, Gore JC. Effects of cell volume fraction changes on apparent diffusion in human cells. *Magn Reson Imaging*. (2000) 18:689–95. doi: 10.1016/S0730-725X(00)00147-8

26. Lin TH, Chiang CW, Perez-Torres CJ, Sun P, Wallendorf M, Schmidt RE, et al. Diffusion MRI quantifies early axonal loss in the presence of nerve swelling. *J Neuroinflammation*. (2017) 14:78. doi: 10.1186/s12974-017-0852-3

27. Lin TH, Zhan J, Song C, Wallendorf M, Sun P, Niu X, et al. Diffusion basis Spectrum imaging detects axonal loss after transient dexamethasone treatment in optic neuritis mice. *Front Neurosci*. (2020) 14:592063. doi: 10.3389/fnins.2020.592063

28. Yang R, Lin TH, Zhan J, Lai S, Song C, Sun P, et al. Diffusion basis spectrum imaging measures anti-inflammatory and neuroprotective effects of fingolimod on murine optic neuritis. *Neuroimage Clin*. (2021) 31:102732. doi: 10.1016/j.nicl.2021.102732

29. Murphy RK, Sun P, Xu J, Wang Y, Sullivan S, Gamble P, et al. Magnetic resonance imaging biomarker of axon loss reflects cervical Spondylotic myelopathy severity. *Spine*. (2016) 41:751–6. doi: 10.1097/BRS.0000000000001337

30. Zhang JK, Jayasekera D, Song C, Greenberg JK, Javeed S, Dibble CF, et al. Diffusion basis Spectrum imaging provides insights into cervical Spondylotic myelopathy pathology. *Neurosurgery*. (2023) 92:102–9. doi: 10.1227/neu.0000000000002183

31. Lin TH, Sun P, Hallman M, Hwang FC, Wallendorf M, Ray WZ, et al. Noninvasive quantification of axonal loss in the presence of tissue swelling in traumatic spinal cord injury mice. *J Neurotrauma*. (2019) 36:2308–15. doi: 10.1089/neu.2018.6016

32. Sauerbeck AD, Fanizzi C, Kim JH, Gangolli M, Bayly PV, Wellington CL, et al. modCHIMERA: a novel murine closed-head model of moderate traumatic brain injury. *Sci Rep*. (2018) 8:7677. doi: 10.1038/s41598-018-25737-6

33. Garber JCB, Bielitzki RW, Clayton JT, Donovan LA, Hendriksen JC, Kohn CF, et al. *Guide for the care and use of laboratory animals*. Washington (DC). The National Academies Press (2011).

34. Lin TH, Kim JH, Perez-Torres C, Chiang CW, Trinkaus K, Cross AH, et al. Axonal transport rate decreased at the onset of optic neuritis in EAE mice. *NeuroImage*. (2014) 100:244–53. doi: 10.1016/j.neuroimage.2014.06.009

35. Lin TH, Spees WM, Chiang CW, Trinkaus K, Cross AH, Song SK. Diffusion fMRI detects white-matter dysfunction in mice with acute optic neuritis. *Neurobiol Dis*. (2014) 67:1–8. doi: 10.1016/j.nbd.2014.02.007

36. Garbow JR, McIntosh C, Conradi MS. Actively decoupled transmit-receive coil-pair for mouse brain MRI. *Concepts Magn Reson Part B Magn Reson Eng*. (2008) 33B:252–9. doi: 10.1002/cmr.b.20124

37. Tu TW, Kim JH, Wang J, Song SK. Full tensor diffusion imaging is not required to assess the white-matter integrity in mouse contusion spinal cord injury. *J Neurotrauma*. (2010) 27:253–62. doi: 10.1089/neu.2009.1026

38. Haldar JP, Wedeen VJ, Nezamzadeh M, Dai GP, Weiner MW, Schuff N, et al. Improved diffusion imaging through SNR-enhancing joint reconstruction. *Magn Reson Med*. (2013) 69:277–89. doi: 10.1002/mrm.24229

39. Wang Y, Sun P, Wang Q, Trinkaus K, Schmidt RE, Naismith RT, et al. Differentiation and quantification of inflammation, demyelination and axon injury or loss in multiple sclerosis. *Brain*. (2015) 138:1223–38. doi: 10.1093/brain/awv046

40. Chiang CW, Wang Y, Sun P, Lin TH, Trinkaus K, Cross AH, et al. Quantifying white matter tract diffusion parameters in the presence of increased extra-fiber cellularity and vasogenic edema. *NeuroImage*. (2014) 101:310–9. doi: 10.1016/j.neuroimage.2014.06.064

41. Wang X, Cusick MF, Wang Y, Sun P, Libbey JE, Trinkaus K, et al. Diffusion basis spectrum imaging detects and distinguishes coexisting subclinical inflammation, demyelination and axonal injury in experimental autoimmune encephalomyelitis mice. *NMR Biomed*. (2014) 27:843–52. doi: 10.1002/nbm.3129

42. Blewitt ES, Pogmore T, Talbot IC. Double embedding in agar paraffin wax as an aid to orientation of mucosal biopsies. *J Clin Pathol*. (1982) 35:365–5. doi: 10.1136/jcp.35.3.365-b

43. Redler Y, Levy M. Rodent models of optic neuritis. *Front Neurol*. (2020) 11:580951. doi: 10.3389/fneur.2020.580951

44. Hylin MJ, Kerr AL, Holden R. Understanding the mechanisms of recovery and/or compensation following injury. *Neural Plast*. (2017) 2017:7125057. doi: 10.1155/2017/7125057

45. Corps KN, Roth TL, McGavern DB. Inflammation and neuroprotection in traumatic brain injury. *JAMA Neurol*. (2015) 72:355–62. doi: 10.1001/jamaneurol.2014.3558

46. Unterberg AW, Stover J, Kress B, Kiening KL. Edema and brain trauma. *Neuroscience*. (2004) 129:1021–9. doi: 10.1016/j.neuroscience.2004.06.046

47. Maxwell WL, Bartlett E, Morgan H. Wallerian degeneration in the optic nerve stretch-injury model of traumatic brain injury: a stereological analysis. *J Neurotrauma*. (2015) 32:780–90. doi: 10.1089/neu.2014.3369

48. Au NPB, Ma CHE. Neuroinflammation, microglia and implications for retinal ganglion cell survival and axon regeneration in traumatic optic neuropathy. *Front Immunol*. (2022) 13:860070. doi: 10.3389/fimmu.2022.860070

49. Stahl A, Hosten N. Trauma to the eye: diffusion restriction on MRI as a surrogate marker for blindness. *Tomography*. (2023) 9:413–9. doi: 10.3390/tomography9010033

50. Wehrl HF, Bezrukov I, Wiehr S, Lehnhoff M, Fuchs K, Mannheim JG, et al. Assessment of murine brain tissue shrinkage caused by different histological fixatives using magnetic resonance and computed tomography imaging. *Histol Histopathol*. (2015) 30:601–13. doi: 10.14670/HH-30.601

51. Bodanapally UK, Shanmuganathan K, Shin RK, Dreizin D, Katzman L, Reddy RP, et al. Hyperintense optic nerve due to diffusion restriction: diffusion-weighted imaging in traumatic optic neuropathy. *AJNR Am J Neuroradiol*. (2015) 36:1536–41. doi: 10.3174/ajnr.A4290

52. Qiu J, Boucher M, Conley G, Li Y, Zhang J, Morriss N, et al. Traumatic brain injury-related optic nerve damage. *J Neuropathol Exp Neurol*. (2022) 81:344–55. doi: 10.1093/jnen/nlac018

53. Khan RS, Ross AG, Aravand P, Dine K, Selzer EB, Shindler KS. RGC and vision loss from traumatic optic neuropathy induced by repetitive closed head trauma is dependent on timing and force of impact. *Transl Vis Sci Technol*. (2021) 10:8. doi: 10.1167/tvst.10.1.8

54. Sujanthan S, Shmuel A, Mendola JD. Visually driven functional MRI techniques for characterization of optic neuropathy. *Front Hum Neurosci*. (2022) 16:943603. doi: 10.3389/fnhum.2022.943603

55. Sujanthan S, Shmuel A, Mendola JD. Resting-state functional MRI of the visual system for characterization of optic neuropathy. *Front Hum Neurosci*. (2022) 16:943618. doi: 10.3389/fnhum.2022.943618

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History of concussion and lowered heart rate variability at rest beyond symptom recovery: a systematic review and meta-analysis

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Introduction: Concussion is a growing concern in worldwide sporting culture. Heart rate variability (HRV) is closely tied with autonomic nervous system (ANS) deficits that arise from a concussion. The objective of this review was to determine if a history of concussion (HOC) can impact HRV values in the time-domain in individuals at rest. This review works to add to the literature surrounding HRV testing and if it can be used to check for brain vulnerabilities beyond the recovery of concussion symptoms.

Materials and methods: The systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method. A computer based systematic review scanned articles dating from 1996 to June 2023 through PubMed, Cochrane Library, Google Scholar, and EMBASE databases. A risk of bias assessment was conducted using the ROBINS-E tool. The average difference in time between heartbeats (MeanNN), the standard deviation of the differences (SDNN), and the root mean squared of the successive intervals (RMSSD) were measured.

Results: Six total studies were found that fit the inclusion criteria including a total of 242 participants (133 without HOC, 109 with HOC). The average age of the control group was 23.3 ± 8.2, while the average age of the history of TBI group was 25.4 ± 9.7, with no significant difference between the groups ($p = 0.202$). Four of the studies reported no significant difference in any of the three measures, while two of the studies reported significant difference for all three measures. The meta-analysis was conducted and found that MeanNN ($p = 0.03$) and RMSSD ($p = 0.04$) reached statistical significance, while SDNN did not ($p = 0.11$).

Conclusion: The results of this meta-analysis showed significant difference in two of the three HRV time-domain parameters evaluated. It demonstrates that there can be lowered HRV values that expand beyond the recovery of symptoms, reflecting an extensive period of ANS susceptibility after a concussion. This may be an important variable in determining an athlete's return to play (RTP). Lack of homogenous study populations and testing methods introduces potential for bias and confounding factors, such as gender or age. Future studies should focus on baseline tests to compare individuals to themselves rather than matched controls.

KEYWORDS

HRV, heart rate variability, history of concussion, TBI, sports concussion

1 Introduction

Traumatic Brain Injury (TBI) is an extremely relevant worldwide health issue, with an increasing concern for its continuous impact on the personal, social, and economic wellbeing of the population. Although the prevalence of TBI's can differ by region, globally around 30 million new TBI's are sustained every year, and it is predicted that many more go unreported (1, 2). The two most common mechanisms of injury are falls and road traffic accidents (2). Various tests and scales are used to measure severity of a TBI, yet the Glasgow Coma Scale tends to be the most popular indicator of whether an injury is classified as mild, moderate, or severe. Moderate (GCS score of 9–12) and severe (GCS score of 8<) are far less common but lead to more complications and an increased mortality risk (1, 2). Mild TBI, also known as concussion, (GCS score of 13–15) is by far the most common, accounting for 80–90% of cases (1, 3). Concussion, is also a common sports injury, with an estimated 1.6–3.8 million reported cases in the United States each year (4). Sports related concussions, are a crucial aspect to consider, due to the potential risk of long-lasting effects on brain and cognitive health (1, 5, 6).

In today's sporting culture, one that promotes strength and toughness by playing through injuries, it is essential to monitor instances of head trauma due to the severity of damage that can result if it is not taken seriously. One example of this is second impact syndrome, which refers to a life-threatening condition that occurs when a second head injury is sustained prior to the full recovery of the initial injury (3, 7). Although often resulting from concussive impacts, edema, contusions, and hematomas are separate forms of TBI, involving brain hemorrhage that may not be present in a simple concussion. In other severe instances, a harsh twisting or shaking of the brain can cause axonal injuries that can deteriorate neural connections and function. Whether it be a concussion or some other form of TBI, many collegiate and professional athletes tend to downplay any symptoms they may have, in fear of losing playing time and opportunities (8, 9). Other important aspects to consider are the intracranial pressure (ICP) and the cerebral perfusion pressure (CPP). ICP is the pressure within the cranium, and CPP is the pressure threshold that allows oxygen to enter cerebral tissue. If a head injury were to occur that results in an increase of ICP that exceeds the CPP pressure gradient, there will be no blood flow to the brain. This will quickly result in life threatening conditions and lead to neuronal death. ICP and its effects on CPP are tied in with sympathetic activity (10), thus, heart rate and changes in HRV have been shown to be predictors of ICP levels (11). Regardless of the cause, the potentially catastrophic situation created by an ignorance to a head injury highlights the importance of in-depth and accurate evaluations for sports trainers and professionals that are working with these athletes.

One physiological marker that has gained more following in the past 20 years or so is heart rate variability (HRV). HRV measures the time between heart beats, specifically the time between the R intervals, and has many other metrics that can be measured as well. These can be divided into time-domain, frequency-domain, and non-linear HRV measures. Time-domain interval metrics look at the variability in measurements in period between successive heartbeats, while frequency-domain interval metrics consider the distribution of signal energy during a heartbeat (12, 13). Non-linear HRV metrics consider the complexity and unpredictability of the heartbeat (12). HRV can also be broken down and measured in different time frames: Ultra short term (<5 min), short term (~5 min) and long term (up to 24 h). Longer term measures of HRV have been more thoroughly implemented into health monitoring, however, short term measures have recently been proven to be just as effective. Despite some initial uncertainty regarding the time required to obtain an accurate reading for HRV measurements, numerous studies investigating this problem further have supported the idea that testing only requires a few minutes or less to produce accurate readings of some HRV metrics (14–16).

Although HRV monitoring is not very well integrated into the athletic community, the drastic increase in widely accessible and simple technology that can accurately test for this metric, such as smartwatches or other handheld devices (17–19), have made HRV more easily recorded and thus becoming a prominent physiological marker used to analyze various health conditions. Not only is this important to an athlete's overall well-being, but studies have begun to draw a link between changes in HRV and head trauma, claiming that autonomic nervous system (ANS) irregularity is a common effect of head trauma in most instances. Despite some conflicting evidence regarding this finding (5, 6, 20), much of the research supports the idea that HRV and brain health go hand in hand. Given that heart rate variability responds to changes in the autonomic nervous system, it can often be used as a measure for ANS functionality. Therefore, decreased ANS from a TBI may be detectable through HRV measurements, making HRV a reliable test for TBI. Both a 2023 meta-analysis and randomized controlled trial investigated how HRV biofeedback treatment was able to improve brain function after a TBI. They found improvements in both emotional and cognitive function, including the reduction of symptoms such as headaches and sleep disturbances (21, 22). HRV can reveal that ANS is still unrecovered well beyond the recovery of symptoms, and taking this into account can prevent susceptible athletes from returning to play and risking repetitive head trauma before full recovery.

Despite evidence supporting the idea that ANS functionality can remain depressed long term after a concussion, few studies testing history of concussion can confirm a relationship between the two. Hence, our systematic review aims to answer whether HRV and ANS functionality at rest are altered when an athlete has a history of concussions. The scope of this study will focus on time-domain parameters, due to the accuracy of short term HRV tests on these measures. The goal is to add to the current pool of literature revolving HRV testing at rest and determine if it is a reliable way to test for cognitive deficits in athletes when deciding when they are ready to return to play.

2 Materials and methods

2.1 Search strategy

PubMed, Google Scholar, Cochrane Library, and EMBASE search engines were used to perform a systematic review using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. These databases were searched by two authors (EW and ZA) for material dating back to 1996, when the Task Force

of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology first defined heart rate variability into its domains. All studies from then up to July 2023 were considered. Searches were conducted using a combination of various keywords, synonyms, headings (MeSH) and entry terms such as: "hrv" or "heart rate variability," "concussion" or "sports concussion," "tbi" or "traumatic brain injury," and "history of concussion."

2.2 Selection criteria

Only studies dealing with the impact of concussion history on HRV values at rest were considered for this meta-analysis. There was no limit on the time or location of publishing, or the types of studies conducted. Only studies in English were recovered. The eligibility criteria were: (1) studies including participants with an average age range of 13–40; (2) must include resting HRV values for both subjects with concussion history, and subjects without concussion history, in at least one time-domain parameter; and (3) Short term/ultra short term HRV must be measured with an electrocardiogram, however there was no specification as to what devices were allowed. Exclusion criteria were (1) studies involving subjects with a history of chronic health conditions; (2) studies done on those were had a history of moderate or severe TBI as defined by the Glasgow Coma Scale; and (3) participants have sustained a concussion within the past 4 months. The article searching process is shown below in accordance with the criteria. Four studies were excluded in the last process. These four studies fit the inclusion criteria; however, they were either unclear with data presentation, or they isolated the data too much with variables (gender, age) unlike the others.

2.3 Risk of bias assessment

A risk of bias assessment was conducted using the ROBINS-E tool. Risk of bias against the seven domains was assessed by two authors (EW and ZA) and any discrepancies were resolved through discussion.

2.4 Statistical analysis

A meta-analysis was conducted from at least three studies that reported data in a homogenous way. In the meta-analysis, the impact of history of concussion was assessed using an electrocardiogram to measure HRV values at rest for the time-domain parameters NN (RR; interval between successive heart beats), SDNN (standard deviation of the NN (RR)), and RMSSD (root mean square of successive RR interval differences). The difference in values and significance levels were then used to determine if there is a notable difference in HRV values for the two groups. We used Review Manager (RevMan 5.4, Cochrane Informatics & Technology, London, UK) to determine the Q and I^2 statistics (in percentages) to establish variation between the studies attributed to heterogeneity. The meta-analysis was conducted using the continuous data function employing a random effects model and reporting mean difference. Where a meta-analysis was not possible, a narrative synthesis approach was used to analyze the data.

3 Results

3.1 Study selection

The search strategy identified 478 articles through the data search. Only 205 records remained after duplicates were removed and 195 studies were excluded. After title and abstract screening, 10 studies remained from which four were excluded after full text reading, leaving six studies for the narrative synthesis (Figure 1).

3.2 Study characteristics

A summary of the study characteristics, including demographics, tested parameters, and general conclusions are listed below in Table 1. All the included studies were controlled trials however they were not randomized, due to the inability to randomly assign a history of concussion to a subject. Therefore, the testers knew who had a history of concussion and who did not.

There were a total of 242 subjects included in the studies; 109 subjects had a history of at least one concussion, while 133 subjects in the control group had no history of concussion. The average age of the control group was 23.3 ± 8.2, while the average age of the history of TBI group was 25.4 ± 9.7. There was no significant statistical difference between the two groups (p-value <0.202). Four of the six studies included females (23, 24, 27, 28) and none of them separated the values by gender. Only 31 of the total 242 subjects were confirmed to be female. Due to this inconsistency and lack of representation, this analysis was unable to determine differences in HRV on a gender basis. Half of the studies included all three tested metrics as outcomes measures, while the other half included either one or two of the tested metrics.

3.3 Risk of bias assessment

Four of the six studies were judged as having low risk of bias with two studies judged as having some risk or high risk of bias (Figure 2). Overall, one third of the articles had some concerns or high risk of bias, with the high risk of bias occurring in domain 6 (risk of bias arising from measurement of the outcome). One third of the studies had a high risk of bias in domain 1 (risk of bias due to confounding). One study each also possessed some concerns in domain 4 and 5.

3.4 Results of studies

Only two of the studies found statistical significance at rest between those with a concussion history, and those without. Hilz et al. in their 2011 study (24) found a significant difference at rest for all three metrics: Mean NN ($p < 0.006$), SDNN ($p < 0.005$), and RMSSD ($p < 0.043$). In a similar study conducted 5 years later, Hilz et al. again demonstrated in their 2016 study (23) that when laying in a supine position, resting values for the history of concussion group were statistically significant in SDNN ($p < 0.043$), and RMSSD (0.005). The authors note that the Mean NN values for the history of concussion group were lower on average than the controls, however it never reached significance ($p < 0.17$). Neither of the other four studies found

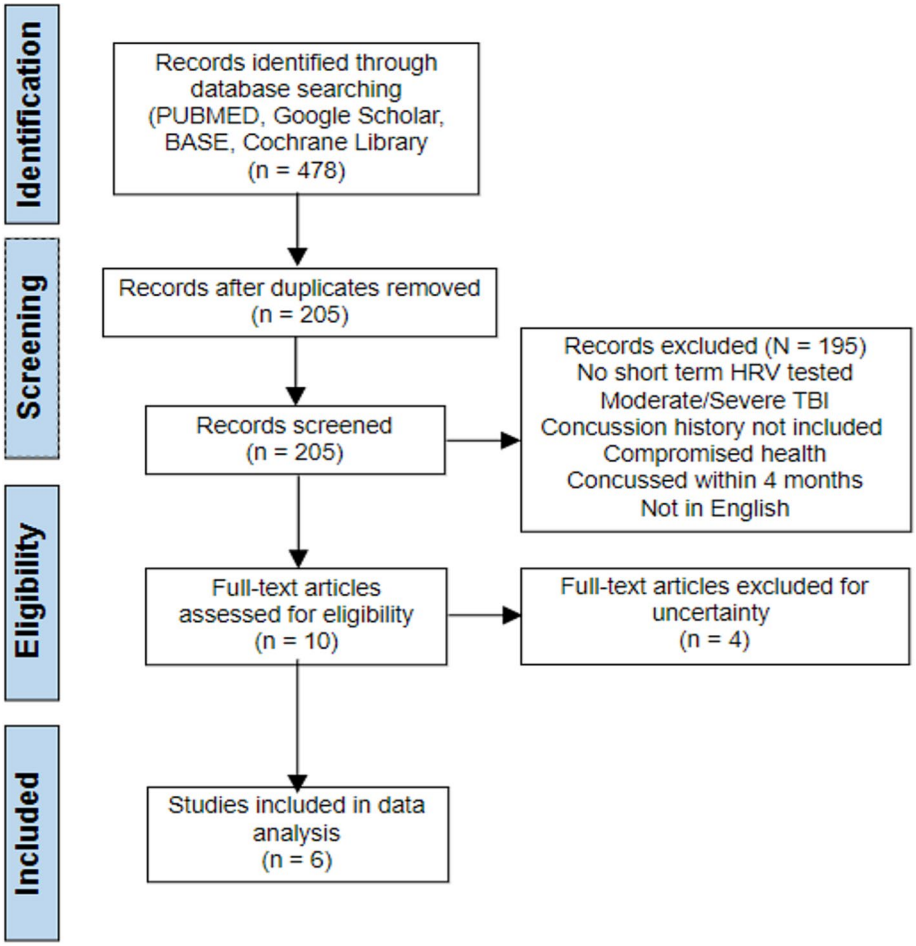

FIGURE 1
PRISMA flow chart.

any notable difference at rest at $p < 0.05$ for any of the three metrics focused on in this analysis.

Meta analysis for studies reporting Mean NN found the mean difference between the TBI and control groups favored TBI with a significant mean difference of −39.47, 95% CI [−75.63, −3.31], $p = 0.03$ (Figure 3). One of the studies did not include MeanNN as a metric (25). These values indicate that MeanNN at rest was significantly lower in those with a history of concussion compared to those without a history of concussion.

Meta analysis for studies reporting data on Mean SDNN found the mean difference between the TBI and control groups was not significant, with a mean difference of −8.28, 95% CI [−18.37, 1.82], $p = 0.11$ (Figure 4). Two out of the six studies did not include SDNN as a metric (27, 28). These values indicate that the SDNN of the group with no history of concussion was not significantly different than the SDNN of the group with a history of concussion.

Meta analysis for studies reporting data on Mean RMSSD found the mean difference between the two groups favored TBI with a significant mean difference of −10.43, 95% CI [−20.43, −0.43], $p = 0.04$. One out of the six studies did not include RMSSD as a metric (Figure 5) (27). These values indicate that the RMSSD of the group with no history of concussion was significantly higher than the RMSSD of the group with a history of concussion.

4 Discussion

This systematic review was conducted to decipher the impact that a history of concussion can have on resting HRV values. Short term and ultra short term HRV methods were utilized to measure resting HRV values. The three time-domain parameters of HRV included were MeanNN, SDNN, and RMSSD. After researching various databases, six total studies consisting of 242 subjects (109 HOC, 133 healthy) were analyzed. Based on the information collected, it was found that a history of concussion was a significant factor in influencing HRV values at rest for MeanNN and RMSSD, but not SDNN. While at rest, MeanNN and RMSSD were shown to present significantly different values between controls and history of concussion subjects, however SDNN did not reach significance. These results were closely in line with two of the six individual studies. Hilz et al. in 2011 found all three of the studied parameters to be statistically lowered in the history of concussion group. They write that the TBI patients had higher resting heart rate, yet a reduced ability to modulate their heart rate, shown in the significantly lowered HRV values (23, 24). However, the other four studies did not conclude a similar thing and were unable to find a find a difference in these parameters at rest.

RMSSD has been linked strongly to the variance in heart beats, and it helps estimate the changes in HRV caused by the vagus nerve

TABLE 1 Characteristics of the studies.

Study	Subjects (n)	Mean age (years)	HRV metrics tested (in time-domain)	Findings (at rest)
Hilz (2016) (23)	Healthy-29 (9 women) TBI-25 (7 women)	Healthy- 31.3 ± 12.2 TBI-35 ± 13.2	MeanNN, SDNN, RMSSD	SDNN and RMSSD lower in history of concussion group (seated)
Hilz (2011) (24)	Healthy-20 TBI-20 (3 women)	Healthy-25.6 ± 8.8 TBI-37 ± 13.3	MeanNN, SDNN, RMSSD	MeanNN, SDNN and RMSSD lower in history of concussion (supine)
Memmini (2021) (25)	Healthy-18 (male) TBI-15 (male)	Healthy-16 ± 1 TBI-16 ± 1	SDNN, RMSSD	No significant difference in SDNN or RMSSD (seated)
Harrison (2022) (26)	Healthy-18 (male) TBI-16 (male)	Healthy-15.98 ± 0.62 TBI-16.06 ± 0.73	MeanNN, SDNN, RMSSD	No significant difference for any metric (seated)
Hilz (2015) (27)	Healthy-27 TBI-24 (7 women)	Healthy-30 ± 11 TBI-34 ± 12	MeanNN	No significant difference in MeanNN between groups (supine)
Haider (2020) (28)	Healthy-21 TBI-9 (5 female)	Healthy-18.3 ± 2.0 TBI-16.7 ± 3.0	MeanNN, RMSSD	No significant difference in either metric (supine)

(29). Due to this strong connection between RMSSD and the actions of the vagus nerve, Hilz writes that "These changes at rest imply a reduced ability of mTBI patients to modulate and buffer bursts of sympathetic activation" (24). The reduced overall HRV puts the post-TBI subjects at risk for sympathetic hyperactivity, further attributing the reduced HRV values to an imbalance between the sympathetic and parasympathetic systems. This finding was repeated in their 2016 study (23). The impact of concussion on the vagus nerve capabilities and sympatho-vagal processes to monitor the ANS long term has been also noted in other previous studies (30–32). Vagal functioning is also closely linked to other neurological conditions. Epilepsy, migraines, dementia, etc. have all been shown to worsen due to a lowered HRV. Concussion frequency and severity can influence the development of these conditions, and although the degree of HRV decreases can differ based on factors such as the severity of a TBI, the negative impact that a lower HRV has on health remains the same whether it is caused by a TBI or some other neurological disease (33). Despite the authors writing that concussion is tied to ANS deficits, the other studies in this meta-analysis found no difference in values at rest and conclude that only in the presence of stressors will the ANS and HRV deficits become known (27, 30, 34). Although not fully understood why this is the case, Gall et al. suggests that "the relatively mild neurological damage suffered as a result of a concussion may be insufficient to induce a detectable neuroautonomic cardiovascular dysfunction at rest" (34). This statement is supported by Katz-Leurer et al. who tested patients with history of severe TBI against healthy controls (35). Although it is beyond the scope of this analysis, researching literature involving moderate and severe TBI may further reveal a difference between a history of mild TBI and a history of more severe cases.

SDNN did not show a significant difference between the two groups with the data collected. This contradicts two of the studies conducted by Hilz et al. who found SDNN to be significantly lower in the history of concussion group compared to the healthy controls (23, 24). SDNN has been highly correlated with activation of both the parasympathetic and sympathetic nervous systems and although it can give accurate readings in short term tests, it is a stronger predictor of health when it comes to 24-h recordings (13). It is a better indicator of slower cardiovascular processes and how the body reacts to various stimuli. This may explain why no significant difference was found in the short-term measurements used in this analysis. It is important to touch on the sensitivity of HRV measurements because short term and ultra short term HRV metrics are not free of flaws and could be responsible for impacting the results. These quicker tests can be affected by transitional effects occurring with in the body (36), and some of the slower heart fluctuations cannot be read (19, 36, 37). Similarly, there is a difference regarding the position in which one is resting that can have an impact on the HRV measurements as well. Three of the studies specified that the resting position was supine (24, 27, 28). Hilz et al. showed significant differences between standing and sitting values in both MeanNN and SDNN despite both positions being in the resting state (24). This difference was shown in another study, when comparing sitting resting values to standing resting values (37). These slight changes in the orientation of the body can change the load on the cardiovascular system, which can impact HRV measurements drastically. Pairing that with a more sensitive metric such as SDNN, it may explain the lack of significance in resting SDNN values between the groups.

One thing that was not specified in the inclusion criteria for this analysis was the number of prior concussions in the TBI groups. Although three of the studies included the number of prior concussions in the demographics (25, 26, 28), only one of the included studies conducted an analysis to stratify the groups by number of prior concussions, to find out if the deficits to HRV last longer or are more prominent as the number of prior concussions increases. They conclude that those with a history of two or more concussion may be susceptible to long-term or even permanent alterations in ANS neurotransmission, and that a history of multiple concussions may negatively impact recovery of the ANS after a bout of exercise (25). Contrarily, this is not shown to be the case in other studies that found no significant difference (38). Furthermore, mechanisms of the HRV changes were neither included in the criteria, nor specifically noted in the studies. HRV can be impacted by things such as inflammation, with the increase of pro-inflammatory cytokines presenting a negative association with HRV (39). Similarly, intracranial pressure and its impact on perfusion and blood flow play a role as well (11).

Due to cardiovascular processes increasing with exercise, another prominent issue is the ability to measure HRV during these times, with some researchers questioning the accuracy of short-term readings during physical activity (15, 16, 40). When measuring for

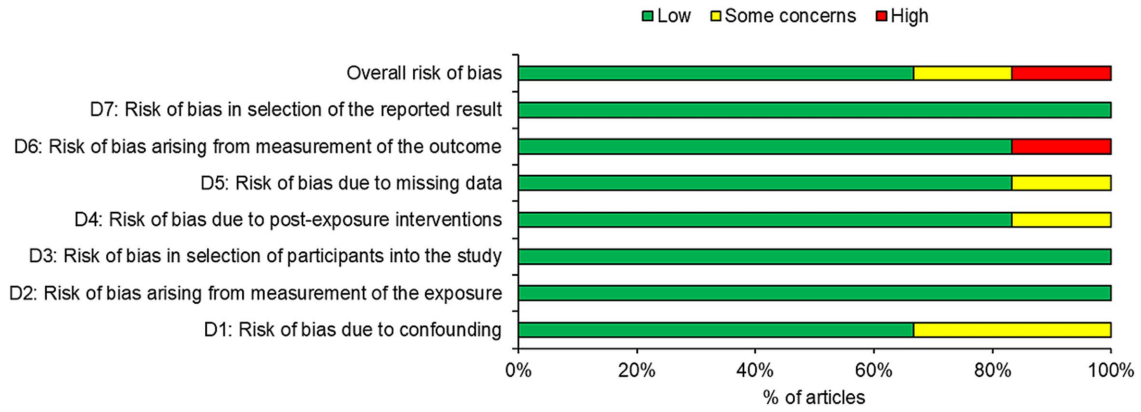

FIGURE 2
Risk of bias in the included studies.

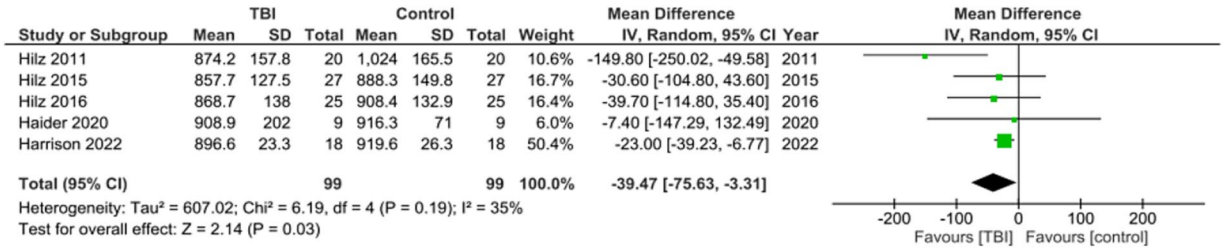

FIGURE 3
Meta-analysis for Mean NN between TBI and control groups.

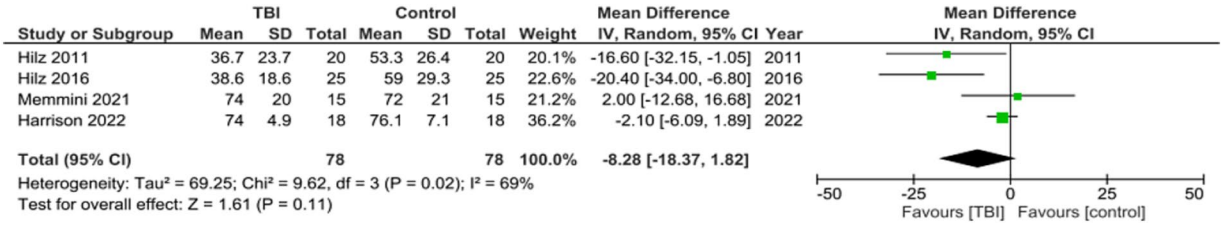

FIGURE 4
Meta-analysis for Mean SDNN between TBI and control groups.

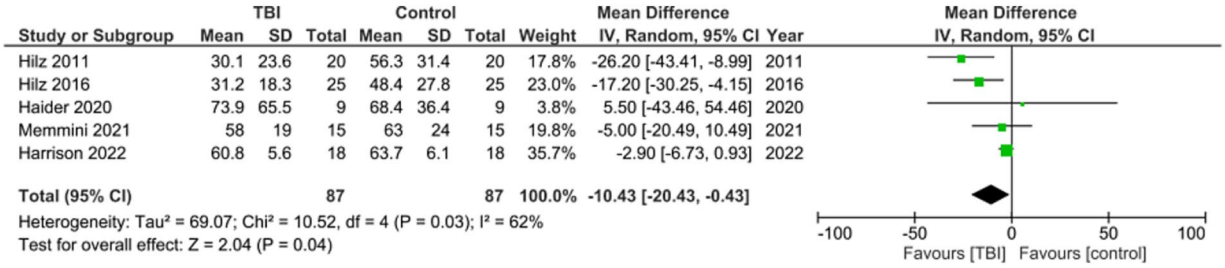

FIGURE 5
Meta-analysis for mean RMSSD between TBI and control groups.

altered HRV, differences are potentially much more present during activity compared to rest and may not be detectable at all without some form of exercise (5, 23, 30). Exercise HRV has been shown to increase during exercise in all groups. However, individual differences in HRV parameters between concussed and non-concussed groups may be more prominent during exercise when compared to rest. La Fountaine found lowered HRV levels during the acute stage in concussed individuals during a handgrip exercise that was not found during rest (41). Abaji et al. followed a similar exercise protocol and found that during physical exertion, concussed patients had a reduced HRV response in both time and frequency-domain parameters, even in the post-acute stage after symptoms have gone (30). A more demanding cycle ergometer test was used to investigate this idea by Gall et al. (34) to see if the results held true. They found no difference in resting values in any parameter of HRV, however, concussed subjects demonstrated lower MeanNN and other frequency parameters during the cycle exercise protocol. Touched on by some of these studies, the differences found through these experiments may not be completely true. Some compounding factors such as detraining effects from taking time off to heal from a concussion, or differing fitness levels between the concussed subjects and their matched healthy controls could account for some of the HRV differences (24, 25, 28). To further prove this concept, a more consistent exercise protocol amongst studies would be crucial. That was not the case for this analysis, so comparing them based on exercise HRV values would have been inappropriate.

Although this analysis focused on the longer-term effect of a history of concussion on autonomic nervous system functionality, there is stronger evidence to suggest that concussion has greater effects on the ANS in the more acute stages. Ellingson et al. found SDNN to be depressed after a 5-min ECG recording in collegiate aged athletes 1–5 days post-concussion (42). Another study on Canadian hockey players found that while standing at rest, the concussed group had lower SDNN and nearly significant lowered RMSSD (31). Two similar studies investigated differences in HRV parameters immediately after concussion, during exercise while asymptomatic, and 1-week post return to play and compared the results to healthy matched controls. One study found the concussed group to be lower in various frequency parameters, and that history of concussion may play a role in this (43). The other also found significant differences in some frequency measures, however also demonstrated lowered MeanNN and SDNN in concussed individuals (44). Regardless of the individual findings, both studies confidently concluded that the resolution of symptoms does not reflect recovery of the ANS, and that significant HRV abnormalities can remain even after return to play. In other forms of TBI, there may be additional lasting consequences to ANS functionality, such as neural damage from brain hemorrhage or torn axons.

5 Limitations

This systematic review has several limitations. One such limitation is the lack of homogeneity of the studies regarding gender inclusion. Although four of the six studies included women (23, 24, 27, 28), none separated males and females into their own groups. This introduces some uncertainty in the results, as gender has been previously shown to occasionally influence HRV values at rest (36, 45, 46). Despite the results not always being significant, it is still important to consider but was not implemented into this analysis. Age can play a similar role in influencing HRV, with elderly populations proven to have a reduced HRV, due to the lowered health status that comes with aging (6, 21, 24). The included studies did combat this potential factor by ensuring there was no significant age difference between the TBI and control groups, so any underlying influence that age would have on the experiment would be evenly distributed between the two groups. When it comes to the age difference between studies, one study had an age range of 18–59 (24), while others focused on young male athletes aged around 16 (25, 26). Finding a more homogenous population in age and gender would help minimize any such differences.

When considering the history of concussion, some of the information in these studies was self-reported. This creates uncertainty regarding the truth to the number of reported concussions, along with recall bias as to how long ago the concussions occurred. Another limitation in most HRV studies is the lack of a baseline test prior to head trauma. Although studies use healthy, age and sex matched controls to make HRV values as comparable as possible, there is a level of assumption that is unable to account for the individuality in HRV values from one person to the next. Fitness levels can play a role in altering HRV (47–49), and genetic factors can also impact these values slightly (36, 50). Other conditional variables include anxiety levels, stress, and emotional states (21, 51, 52). Future studies regarding HRV should start with baseline tests for all athletes in the subject population, allowing comparisons to be made individually, to better display how a history of concussions can affect HRV values.

6 Conclusion

In conclusion, this meta-analysis investigated if a prior history of concussion had a lasting long-term effect on HRV values. The implications of the material were to further investigate whether HRV can be used to test ANS functionality and be used on athletes to determine if they are able to return to play. Resting HRV values in the time-domain were researched for the metrics of MeanNN, SDNN, and RMSSD. Six studies were included, and the results showed a significant difference in resting values between the two groups in MeanNN and RMSSD. History of concussion may lower HRV at rest, therefore it is important to consider when evaluating a concussed athlete. History of concussion may hint at an increasingly compromised ANS and could help prevent a vulnerable athlete from returning to play prematurely. Factors such as age, gender, or time since last concussion could have played a role in influencing results. Inconsistencies between studies lingered, so future studies should find a standardized procedure and more homogenous study group to confirm any relationship.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

EW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. ZA: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. VP: Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol*. (2022) 21:1004–60. doi: 10.1016/S1474-4422(22)00309-X

2. James SL, Theadom A, Ellenbogen RG, Bannick MS, Montjoy-Venning W, Lucchesi LR, et al. 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. doi: 10.1016/S1474-4422(18)30415-0

3. Laskowski RA, Creed JA, Raghupathi R. Chapter 4: pathophysiology of mild TBI. In Kobeissy FH Ed. *Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects*. Boca Raton: CRC Press/Taylor and Francis; (2015).

4. Abrahams S, Mc Fie S, Patricios J, Posthumus M, September AV. Risk factors for sports concussion: an evidence-based systematic review. *Br J Sports Med*. (2014) 48:91–7. doi: 10.1136/bjsports-2013-092734

5. Charron J, Soto-Catalan C, Marcotte L'Heureux V, Comtois AS. Unclear outcomes of heart rate variability following a concussion: a systematic review. *Brain Inj*. (2021) 35:987–1000. doi: 10.1080/02699052.2021.1891459

6. Blake TA, Mckay CD, Meeuwisse WH, Emery CA. The impact of concussion on cardiac autonomic function: a systematic review. *Brain Inj*. (2016) 30:132–45. doi: 10.3109/02699052.2015.1093659

7. McLendon LA, Kralik SF, Grayson PA, Golomb MR. The controversial second impact syndrome: a review of the literature. *Pediatr Neurol*. (2016) 62:9–17. doi: 10.1016/j.pediatrneurol.2016.03.009

8. Marshall CM. Sports-related concussion: a narrative review of the literature. *Can Chiropractic J*. (2012) 56:299–310.

9. Register-Mihalik JK, Guskiewicz KM, Valovich McLeod TC, Linnan LA, Mueller FO, Marshall SW. Knowledge, attitude, and concussion-reporting behaviors among high school athletes: a preliminary study. *J Athl Train*. (2013) 48:645–53. doi: 10.4085/1062-6050-48.3.20

10. Schmidt EA, Despas F, Pavy-le Traon A, Czosnyka Z, Pickard JD, Rahmouni K, et al. Intracranial pressure is a determinant of sympathetic activity. *Front Physiol*. (2018) 9:11. doi: 10.3389/fphys.2018.00011

11. Mowery NT, Norris PR, Riordan W, Jenkins JM, Williams AE, Morris JA. Cardiac uncoupling and heart rate variability are associated with intracranial hypertension and mortality: a study of 145 trauma patients with continuous monitoring. *J Trauma*. (2008) 65:621–7. doi: 10.1097/TA.0b013e3181837980

12. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health*. (2017) 5:258. doi: 10.3389/fpubh.2017.00258

13. Ziadia H, Sassi I, Trudeau F, Fait P. Normative values of resting heart rate variability in young male contact sport athletes: reference values for the assessment and treatment of concussion. *Front Sport Active Living*. (2023) 4:730401. doi: 10.3389/fspor.2022.730401

14. Shaffer F, Meehan ZM, Zerr CL. A critical review of ultra-short-term heart rate variability norms research. *Front Neurosci*. (2020) 14:594880. doi: 10.3389/fnins.2020.594880

15. Esco MR, Flatt AA. Ultra-short-term heart rate variability indexes at rest and post-exercise in athletes: evaluating the agreement with accepted recommendations. *J Sport Sci Med*. (2014) 13:535–41.

16. Nussinovitch U, Elishkevitz KP, Katz K, Nussinovitch M, Segev S, Volovitz B, et al. Reliability of ultra-short ECG indices for heart rate variability. *Ann Noninvasive Electrocardiol*. (2011) 16:117–22. doi: 10.1111/j.1542-474X.2011.00417.x

17. Chen YS, Lu WA, Pagaduan JC, Kuo CD. A novel smartphone app for the measurement of ultra–short-term and short-term heart rate variability: validity and reliability study. *JMIR Mhealth Uhealth*. (2020) 8:e18761. doi: 10.2196/18761

18. Moya-Ramon M, Mateo-March M, Peña-González I, Zabala M, Javaloyes A. Validity and reliability of different smartphones applications to measure HRV during short and ultra-short measurements in elite athletes. *Comput Methods Prog Biosci*. (2022) 217:106696. doi: 10.1016/j.cmpb.2022.106696

19. Hernando D, Roca S, Sancho J, Alesanco Á, Bailón R. Validation of the apple watch for heart rate variability measurements during relax and mental stress in healthy subjects. *Sensors*. (2018) 18:2619. doi: 10.3390/s18082619

20. Esterov D, Greenwald BD. Autonomic dysfunction after mild traumatic brain injury. *Brain Sci*. (2017) 7:100. doi: 10.3390/brainsci7080100

21. Thayer JF, Åhs F, Fredrikson M, Sollers JJ III, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev*. (2012) 36:747–56. doi: 10.1016/j.neubiorev.2011.11.009

22. Lu HC, Gevirtz R, Yang CC, Hauson AO. Heart rate variability biofeedback for mild traumatic brain injury: a randomized-controlled study. *Appl Psychophysiol Biofeedback*. (2023) 48:405–21. doi: 10.1007/s10484-023-09592-4

23. Hilz MJ, Lui M, Koehn J, Wang R, Ammon F, Flanagan SR, et al. Valsalva maneuver unveils central baroreflex dysfunction with altered blood pressure control in persons with a history of mild traumatic brain injury. *BMC Neurol*. (2016) 16:61. doi: 10.1186/s12883-016-0584-5

24. Hilz MJ, DeFina PA, Anders S, Koehn J, Lang CJ, Pauli E, et al. Frequency analysis unveils cardiac autonomic dysfunction after mild traumatic brain injury. *J Neurotrauma*. (2011) 28:1727–38. doi: 10.1089/neu.2010.1497

25. Memmini AK, La Fountaine MF, Broglio SP, Moore RD. Long-term influence of concussion on cardio-autonomic function in adolescent hockey players. *J Athl Train*. (2021) 56:141–7. doi: 10.4085/1062-6050-0578.19

26. Harrison A, Lane-Cordova A, La Fountaine MF, Moore RD. Concussion history and heart rate variability during bouts of acute stress. *J Athl Train*. (2022) 57:741–7. doi: 10.4085/1062-6050-0314.21

27. Hilz MJ, Aurnhammer F, Flanagan SR, Intravooth T, Wang R, Hösl KM, et al. Eyeball pressure stimulation unveils subtle autonomic cardiovascular dysfunction in persons with a history of mild traumatic brain injury. *J Neurotrauma*. (2015) 32:1796–804. doi: 10.1089/neu.2014.3842

28. Haider MN, Johnson BD, Horn EC, Leddy JJ, Wilber CG, Reed EL, et al. Blunted cardiac parasympathetic activation in student athletes with a remote history of concussion: a pilot study. *Front Neurol*. (2020) 11:547126. doi: 10.3389/fneur.2020.547126

29. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front Psychol*. (2014) 5:1040. doi: 10.3389/fpsyg.2014.01040

30. Abaji JP, Curnier D, Moore RD, Ellemberg D. Persisting effects of concussion on heart rate variability during physical exertion. *J Neurotrauma*. (2016) 33:811–7. doi: 10.1089/neu.2015.3989

31. Bishop S, Dech R, Baker T, Butz M, Aravinthan K, Neary JP. Parasympathetic baroreflexes and heart rate variability during acute stage of sport concussion recovery. *Brain Inj*. (2017) 31:247–59. doi: 10.1080/02699052.2016.1226385

32. Chang C, Metzger CD, Glover GH, Duyn JH, Heinze HJ, Walter M. Association between heart rate variability and fluctuations in resting-state functional connectivity. *Neuro Image*. (2013) 68:93–104. doi: 10.1016/j.neuroimage.2012.11.038

33. Arakaki X, Arechavala RJ, Elizabeth CH, Bautista J, Bliss B, Molloy C, et al. The connection between heart rate variability (HRV), neurological health, and cognition: a literature review. *Front Neurosci*. (2023) 17:1055445. doi: 10.3389/fnins.2023.1055445

34. Gall B, Parkouse W, Goodman D. Heart rate variability of recently concussed. *Med Sci Sports*. (2004) 36:1269–74. doi: 10.1249/01.MSS.0000135787.73757.4D

35. Katz-Leurer M, Rotem H, Keren O, Meyer S. Heart rate and heart rate variability at rest and during exercise in boys who suffered a severe traumatic brain injury and typically-developed controls. *Brain Inj*. (2010) 24:110–4. doi: 10.3109/02699050903508234

36. Kiss O, Sydó N, Vargha P, Vágó H, Czimbalmos C, Édes E, et al. Detailed heart rate variability analysis in athletes. *Clin Auton Res*. (2016) 26:245–52. doi: 10.1007/s10286-016-0360-z

37. Sandercock GRH, Bromley PD, Brodie DA. The reliability of short-term measurements of heart rate variability. *Int J Cardiol*. (2005) 103:238–47. doi: 10.1016/j.ijcard.2004.09.013

38. Pyndiura KL, Di Battista AP, Hutchinson MG. A history of concussion is associated with minimal perturbations to heart rate variability in athletes. *Brain Inj*. (2020) 34:1416–21. doi: 10.1080/02699052.2020.1802661

39. Williams DP, Koenig J, Carnevali L, Sgoifo A, Jarczok MN, Sternberg EM, et al. Heart rate variability and inflammation: a meta-analysis of human studies. *Brain Behav Immun*. (2019) 80:219–26. doi: 10.1016/j.bbi.2019.03.009

40. Tanoue Y, Nakashima S, Komatsu T, Kosugi M, Kawakami S, Kawakami S, et al. The validity of ultra-short-term heart rate variability during cycling exercise. *Sensors*. (2023) 23:3325. doi: 10.3390/s23063325

41. La Fountaine MF, Heffernan KS, Gossett JD, Bauman WA, De Meersman RE. Transient suppression of heart rate complexity in concussed athletes. *Auton Neurosci*. (2009) 148:101–3. doi: 10.1016/j.autneu.2009.03.001

42. Ellingson CJ, Singh J, Ellingson CA, Sirant LW, Krätzig GP, Dorsch KD, et al. Alterations in Baroreflex sensitivity and blood pressure variability following sport-related concussion. *Life*. (2022) 12:1400. doi: 10.3390/life12091400

43. Senthinathan A, Mainwaring LM, Hutchison M. Heart rate variability of athletes across concussion. *Clin J Sport Med*. (2017) 27:288–95. doi: 10.1097/JSM.0000000000000337

44. Hutchinson MG, Mainwaring LM, Senthinathan A, Thomas S. Psychological and physiological markers of stress in concussed athletes across recovery milestones. *J Head Trauma Rehabilit*. (2016) 32:E38–48. doi: 10.1097/HTR.0000000000000252

45. Flores G, Monteiro D, Silva F, Duarte-Mendes P. Heart rate variability behavior in athletes after a sports concussion: a systematic review. *Scand J Med Sci Sports*. (2023) 33:1598–606. doi: 10.1111/sms.14409

46. Peak BM. *The new science of athletic performance that is revolutionizing sports. 1st* ed Chelsea Green Publishing (2019).

47. Conder RL, Conder AA. Heart rate variability interventions for concussion and rehabilitation. *Front Psychol*. (2014) 5:890. doi: 10.3389/fpsyg.2014.00890

48. Bishop SA, Dech RT, Guzik P, Neary JP. Heart rate variability and implication for sport concussion. *Clin Physiol Funct Imaging*. (2018) 38:733–42. doi: 10.1111/cpf.12487

49. Kupper NHM, Willemsen G, van den Berg M, de Boer D, Posthuma D, Boomsma DI, et al. Heritability of ambulatory heart rate variability. *Circulation*. (2004) 110:2792–6. doi: 10.1161/01.CIR.0000146334.96820.6E

50. Liu K, Jiao Y, Du C, Zhang X, Chen X, Xu F, et al. Driver stress detection using ultra-short-term HRV analysis under real world driving conditions. *Entropy*. (2023) 25:194. doi: 10.3390/e25020194

51. Melillo P, Bracale M, Pecchia L. Nonlinear heart rate variability features for real-life stress detection. Case study: students under stress due to university examination. *Bio Med Eng OnLine*. (2011) 10:96. doi: 10.1186/1475-925X-10-96

52. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: a meta-analysis. *Neurosci Biobehav Rev*. (2016) 64:288–310. doi: 10.1016/j.neubiorev.2016.03.007

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Translational medical bioengineering research of traumatic brain injury among Chinese and American pedestrians caused by vehicle collision based on human body finite element modeling

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Based on the average human body size in China and the THUMS AM50 finite element model of the human body, the Kriging interpolation algorithm was used to model the Chinese 50th percentile human body, and the biological fidelity of the model was verified. We built three different types of passenger vehicle models, namely, sedan, sports utility vehicle (SUV), and multi-purpose vehicle (MPV), and used mechanical response analysis and finite element simulation to compare and analyze the dynamic differences and head injury differences between the Chinese 50th percentile human body and the THUMS AM50 model during passenger vehicle collisions. The results showed that there are obvious differences between the Chinese mannequin and THUMS in terms of collision time, collision position, invasion speed, and angle. When a sedan collided with the mannequins, the skull damage to the Chinese human body model was more severe, and when a sedan or SUV collided, the brain damage to the Chinese human body was more severe. The abovementioned results suggest that the existing C-NCAP pedestrian protection testing regulations may not provide the best protection for Chinese human bodies, and that the regulations need to be improved by combining collision damage mechanisms and the physical characteristics of Chinese pedestrians. This thorough investigation is positioned to shed light on the fundamental biomechanics and injury mechanisms at play. Furthermore, the amalgamation of clinically rooted translational and engineering research in the realm of traumatic brain injury has the potential to establish a solid foundation for discerning preventive methodologies. Ultimately, this endeavor holds the potential to introduce effective strategies aimed at preventing and safeguarding against traumatic brain injuries.

KEYWORDS

traumatic brain injury, medical bioengineering, finite element simulation, pedestrian protection, translational and engineering research

Introduction

Pedestrian accidents have always accounted for a significant proportion of traffic accidents, and have a high incidence of serious injuries and mortality rates. In Europe, 23% of traffic accident fatalities are pedestrians, whereas pedestrians account for 11% of fatalities in traffic accidents in the United States, and that number increases to over 25% in China (1). This means that on average, in China, nearly 25,000 pedestrians die in traffic accidents every year, ranking first among all traffic accidents in the country. Head injury is the main cause of pedestrian death, accounting for approximately 54% of pedestrian traffic accident fatalities (2). Head injury is mainly divided into skull fracture and brain injury, with brain injury being divided into focal brain injury (hematoma, contusion, etc.) and diffuse brain injury (diffuse axonal injury, concussion, etc.).

In recent years, to acquire a better understanding of the mechanisms of injury to pedestrians' skulls and brains, many researchers have developed finite element models of the human head and have used finite element simulations to simulate collisions between passenger vehicles and pedestrians. Watanabe et al. (3) established an SUV pedestrian collision simulation using the THUMS pedestrian finite element model and studied the impact of collision speed on pedestrian head and chest injuries. Tamura et al. (4) developed a finite element model of the brain representing a 50th percentile male and combined it with the THUMS model to explore the mechanism of pedestrian head injury through simulation. Yang et al. (5) and others from Hunan University established a head finite element model containing muscles, spinal cord, and complete brain structure. Wei (6) combined it with the LSTC Hybrid—III finite element model to analyze the impact of different vehicle speeds and pedestrian gait on brain injury.

However, the abovementioned pedestrian collision damage studies were conducted using THUMS human finite element models or Hybrid III dummy finite element models representing European and American anthropomorphic characteristics. There are certain differences in the average human body size between Europe, America, and China, with differences in length, mass, and center of gravity of each body segment leading to differences in pedestrian movement trajectory, head collision angle, position, and degree of injury under the same working conditions, leading to different design goals for pedestrian protection structures. Many countries and institutions have established three-dimensional human body shape measurement databases through optical scanning to obtain more detailed human body data, such as the United Kingdom three-dimensional human body size database in the United Kingdom (7) and the CAESAR database established in North America, the Netherlands, and Italy (8). However, there is currently no authoritative Chinese human body shape measurement database available. Therefore, this article establishes a Chinese standing human body surface model through optical scanning and uses the grid transformation method to establish a finite element model of the Chinese 50th percentile male body. By comparing the impact simulation results of various parts of the body with literature data, their biological fidelity was verified. The mechanism of skull and brain damage in pedestrian collision accidents was analyzed in detail through simulation, and the dynamic response and head injury differences between Chinese and American pedestrians in different passenger vehicle models were compared. The workflow is shown in Figure 1.

Materials and methods

Chinese body finite element modeling

According to the latest statistical results of the Chinese Academy of Standardization on the basic ergonomic parameters of Chinese adults from 2014 to 2019 (9), using the Latin square sampling method, 40 adult male volunteers who met anthropometric and health standards and had no physiological diseases, such as scoliosis, were uniformly selected for three-dimensional optical scanning to generate a body surface model. Reverse engineering software was used to process the initial body surface model with hole repair, surface smoothing, symmetry, etc., and finally obtain the Chinese male body surface model data randomly distributed between the 5 and the 95th percentile.

In anthropometry, the 5, 50, and 95th percentiles are most commonly used, representing small, medium, and large people, respectively. In this study, the 50th percentile male was taken as the representative to compare the difference between Chinese and American human body injuries caused by vehicle collisions. The THUMS AM50 standing human finite element model (version 4.02) was selected to simulate a 50th percentile male human body in Europe and America. This model was developed in collaboration with Toyota Motor Corporation and Toyota Central R&D Labs for pedestrian collision safety research. The model is 1,786 mm tall, weighs 77.6 kg, and has a complete skeletal structure and internal organs. Its biological fidelity has been fully verified (10, 11). The finite element model of Chinese pedestrians was obtained through grid transformation based on the THUMS model and the Chinese 50th percentile human body surface model. Three male volunteers from Henan, Anhui, and Hainan, aged between 22 and 25 years old, whose height and weight were close to the 50th percentile, were selected from the database for average processing to build up an accurate Chinese 50th percentile body surface model. The average process is shown in Figure 1. Averaging the data of the Chinese 50th percentile body surface model, the Kriging interpolation algorithm was used to perform grid transformation on the THUMS pedestrian finite element model and generate the Chinese 50th percentile finite element model.

Verification of actual damage of human finite element model in lateral impact

When a vehicle impacts a pedestrian laterally, the most vulnerable body parts are the head, chest, and lower limbs. Therefore, the injury responses of the Chinese mannequin are tested in the head, chest, and lower limbs parts. See Table 1 for the list and comparison with the simulation results.

A rigid ball impactor with a mass of 1.213 kg and a radius of 48 mm was used to impact the overhead area at an initial speed of 8.0 m/s, simulating the head rigid ball impact test conducted by Yoganandan et al. (12), while fixing the skull base, and recording the force-displacement curve of the impactor. The results of test marks 7–12 were selected as the verification basis for the head impact simulation of the Chinese Mannequin (see Supplementary Material 1).

The head rotated in the side impact direction with 7,400 rad/s2 angular acceleration, simulating the head rotation test of Hardy and Kleiven (13, 14), and we recorded the y and z direction displacement

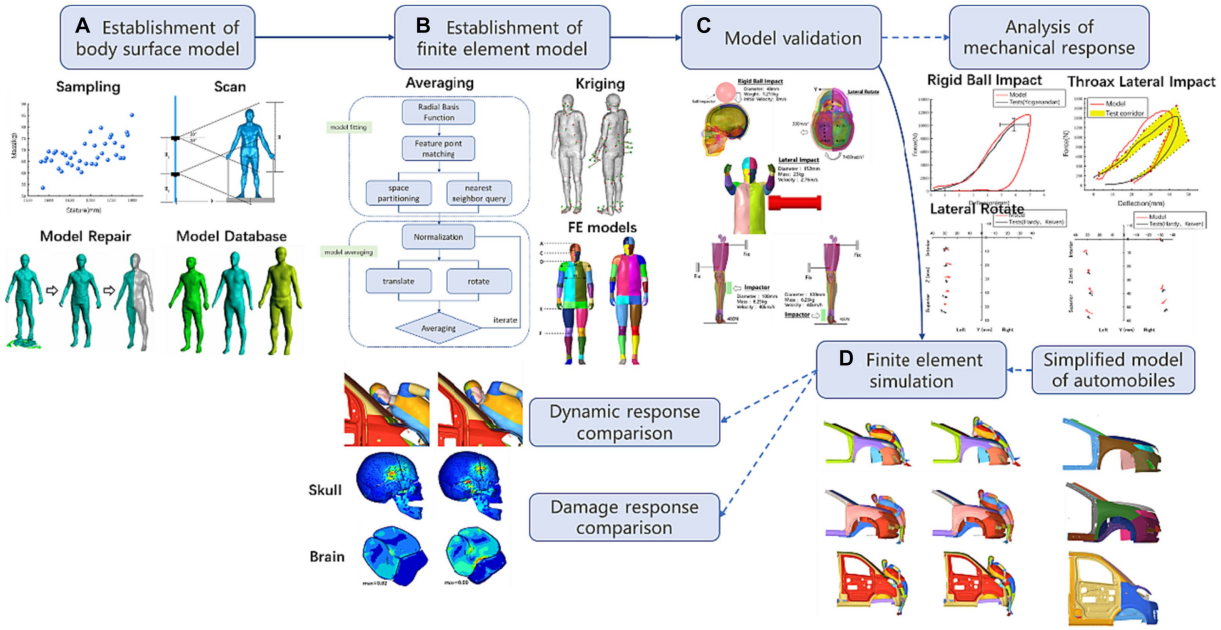


FIGURE 1
The workflow and technology roadmap. **(A)** The process of establishing a database of Chinese male body surface models, **(B)** the process of averaging body surface models and the method of establishing a finite element model of the Chinese 50th percentile male body, **(C)** the simulation verification of the biological fidelity of the finite element model of Chinese 50th percentile human body, and **(D)** the construction of vehicle-pedestrian simulation conditions and the analysis of simulation results.

of each marker point of the brain relative to the skull. Using a cylindrical impactor with a mass of 23 kg and a diameter of 152 mm, we simulated the lateral impact test of Shaw et al. (15) on the human chest at a speed of 2.76 m/s, and recorded the force deformation response curve of the chest.

We fixed the proximal and distal ends of the femur with screws and set a fixation plate near the knee joint at the distal end of the femur to limit the movement of the femur. Then, a preload of 400 N was applied axially from the foot to the tibia, simulating the gravity of the upper body when standing in a human posture. In the shear test, the impactor impacted the lower part of the knee joint from the outside of the leg at a speed of 40 km/h, and in the bending test, the impactor impacted the ankle joint from the inside of the leg at a speed of 40 km/h. The impactor mass of both tests was 6.25 kg, and the impact surface was connected with a 50 mm thick foam material to simulate the bending and shear test of the lower limbs of Kajzer (16, 17). In Kajzer's experiment, the cadaver samples numbered 11B, 12S, 13S, and 14B were all male (see Supplementary Material 2), with an average height and weight of 169 cm and 68 kg, which are similar in size to the Chinese 50th percentile male human body. Therefore, the results of experiments numbered 12S and 13S were selected as controls for shear simulation, and the results of experiments numbered 11B and 14B were selected as controls for bending simulation. The knee bending angle, knee joint bending moment, and initial injury time were compared to Shear displacement and other data.

Statistical method

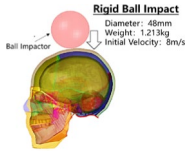
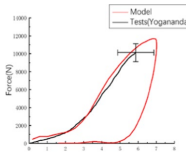
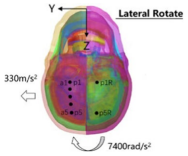
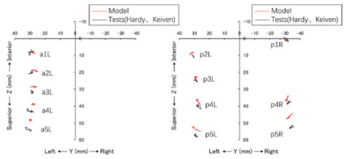
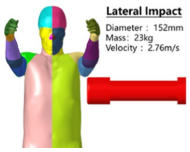
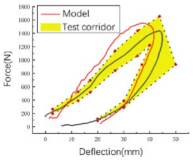
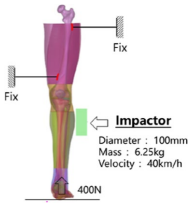
Considering the significant differences in size between cadaver samples and the inability to fully represent the 50th percentile standard human body, the author used the Mertz Viano (18, 19) method to standardize the chest mechanical response curve obtained from the test to generate a chest standard mechanical response curve representing the 50th percentile Chinese human body under a lateral impact (see Supplementary Material 3), and developed a standard response interval using the method of Lobdell (20).

Vehicle modeling with three different basic structures and collision simulation with different mannequins

According to the pedestrian traffic accident database and various pedestrian accident investigation reports (21–23), passenger vehicles account for the highest proportion of pedestrian accidents. Therefore, three different structural shapes, namely, sedans, SUVs, and MPVs, were selected to construct a finite element model of passenger vehicles. The simplified model retains the structure of the A-pillar, windshield, bumper, crash beam, hood, engine, battery, etc., and is positioned at the center of gravity-defined centralized mass. The initial models of the three vehicle models have been validated (24–26).

We performed a simulation using the finite element analysis program LS-DYNATM V971. In the simulation, a speed of 40 km/h was applied to each vehicle model to collide with the Chinese mannequin and the THUMS model. Then, we output the resultant head acceleration of two mannequins, Head Injury Criterion (HIC15) and Brain Injury Criteria (BRIC), with equivalent stress to the skull and maximum principal strain to the brain. Based on the simulation results of different models in China and the United States in collisions with three different types of passenger vehicles, suggestions are given for the C-NCAP pedestrian protection testing procedure. To avoid the randomness of the conclusion, pedestrian collision simulations at speeds of 30 and

TABLE 1 Validation list of the chinese mannequin position.

	Simulation settings	Mechanical response comparison
Head		
		
Chest		
Lower limb		① Bending moment at initial damage moment Test: 369–545 Nm, Simulation: 356 Nm ② Shear force at initial damage time Test: 1.6–2.3KN, Simulation: 2.5KN ③ Knee bending angle Test: 1.7–4.1°, Simulation: 5° ④ Knee shear displacement Test: 13–14 mm, Simulation: 16 mm
		①Bending moment at initial damage moment Test: 367–450 Nm, Simulation: 406 Nm ② Shear force at initial damage time Test: 1.2–1.4KN, Simulation: 2.9KN ③ Knee bending angle Test: 10–14.8°, Simulation: 16° ④ Knee shear displacement Test: 13–17 mm, Simulation: 30 mm

50 km/h were conducted under the same conditions to further validate the conclusion.

Results

Construction and validation of a finite element model of the Chinese human body

The comparison between the Chinese and American mannequins is shown in Figure 2, and the size comparison data are shown in Table 2. The Chinese mannequin is smaller than the THUMS mannequin in size, shoulder width, and chest thickness, and the position of the pelvis, femur, and tibia is also lower. Comparing the output results of various verification simulations with the test results, it was observed that the simulation results were basically within the range of the test results, so the biological fidelity of the Chinese mannequin could be verified.

Vehicle structure simulation and collision simulation

For the test, we maintained two human body models in a standing posture, positioned at the front of the vehicle along the middle line of the vehicle, with their orientation perpendicular to the direction of vehicle travel. Figure 3 shows the relative positions of the front-end shapes of the three vehicle models and various parts of the human body at the initial moment.

Illustration

When the sedan model and the mannequins collided, the head of the Chinese mannequin came into contact with the vehicle at 118 ms with an invasion angle of 81°. The head of the THUMS model came into contact with the vehicle at 128 ms with an invasion angle of 58°. When the SUV model and the mannequins collided, the head of the Chinese mannequin came into contact with the vehicle at 94 ms and the intrusion angle was

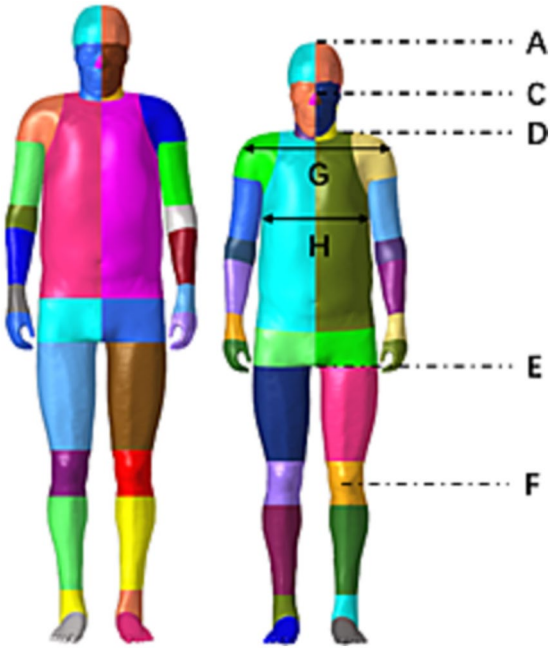


FIGURE 2
Comparison between THUMS and the Chinese Human Body Model (L: THUMS Model, R: Chinese Human Body Model).

87°, whereas the head of the THUMS model came into contact with the vehicle at 104 ms with an intrusion angle of 87°. When the MPV model and the mannequins collided, the head of the Chinese mannequin came into contact with the vehicle at 90 ms with an invasion angle of 51°, and the head of the THUMS model came into contact with the vehicle at 96 ms with an invasion angle of 40°.

Figure 4 shows the trajectory of pedestrians during the collision process of three vehicle models at a speed of 40 km/h. The lower limbs first came into contact with the bumper and accelerated forward under the impact of the vehicle. The upper body rotated in the direction of the vehicle hood due to inertia, causing the buttocks, abdomen, chest, and shoulders to collide with the hood or windshield in sequence. Finally, the head rotated toward the engine hood or windshield for impact. There are three main damage mechanisms in head-to-vehicle collisions: concentrated compressive force, viscous load in the skull, and inertial load in the brain. Concentrated compressive force may lead to skull fractures, and the inertial load during rotation will cause relative motion between the skull and the brain, resulting in a high strain that may cause brain damage. When the same vehicle model collided with two types of human bodies at the same speed, compared to the THUMS, the rotation radius of the buttocks, abdomen, chest, and head of the Chinese human body was smaller, the contact time with the vehicle came earlier, the entire collision process was shorter, and the contact position was also closer to the front. When the sedan collided with the mannequins, the Chinese human head collided with the rear end of the hood and the transition area of the windshield at 118 ms, with intrusion speeds and angles of 81°and 40.4 km/h, respectively, while the THUMS head collided with the windshield

TABLE 2 Comparison of human body model dimensional data.

Size	Chinese 50th percentile body size (male)	Chinese mannequin	THUMS
A. Height	1,690 mm	1,689 mm	1,786 mm
B. Weight	67.6 kg	67.3 kg	77.6 kg
C. Eye level	1,568 mm	1,560 mm	1,659 mm
D. Shoulder height	1,387 mm	1,367 mm	1,481 mm
E. Perineal height	790 mm	790.7 mm	826.4 mm
F. Tibial height	444 mm	442.7 mm	460.1 mm
G. Shoulder width	431 mm	434 mm	446 mm
H. Thorax width	280 mm	288 mm	312 mm

at 128 ms, with intrusion speeds and angles of 58°and 39.9 km/h, respectively. When the SUV model collided with the mannequins, due to the high hood, the Chinese human head collided with the hood at 94 ms, and the THUMS head collided with the high stiffness area at the rear of the hood at 104 ms. Both types of human heads had intrusion angles of 87°. The velocity of the Chinese mannequin's head was 40.8 km/h, while the THUMS model's head velocity was 41.6 km/h. When encountering an MPV collision, the rotation amplitude of the pedestrian's chest was smaller, resulting in earlier head-to-vehicle collisions at lower speeds and angles. The Chinese human head collided with the MPV windshield at a speed and angle of 23.4 km/h and 51°, respectively, at 90 ms, while the THUMS head collided with the windshield at a speed and angle of 23.8 km/h and 40°, respectively, at 96 ms. The collision simulation at different speeds is shown in Figure 5. The results show that although the change in vehicle speed led to changes in the movement trend and injury response of each mannequin, the comparison results of skull injury and brain injury were consistent at 40 km/h.

Table 3 shows the peak response of two types of human head injuries in collisions for each vehicle type at a speed of 40 km/h, with all HIC values higher than the injury standard value of 700. Figure 6 shows the equivalent force cloud map of the skull collision side and the differences in collision position and angle result in different stress distributions in two types of human skulls. Figure 7 shows the principal strain cloud map of the central cross-section of the brain at the moment of maximum principal strain (MPS).

When the sedan model and mannequins collided, the maximum stress on the Chinese mannequin skull was 146 Mpa, which appeared in the occipital bone, and the maximum stress on the THUMS model skull was 104 Mpa, which appeared in the occipital bone. When the SUV model and mannequins collided, the maximum stress on the Chinese mannequin skull was 107 Mpa, which occurred in the occipital bone, and the maximum stress on the THUMS model skull was 122 Mpa, which occurred in the frontal bone. When the MPV model and mannequins collided, the

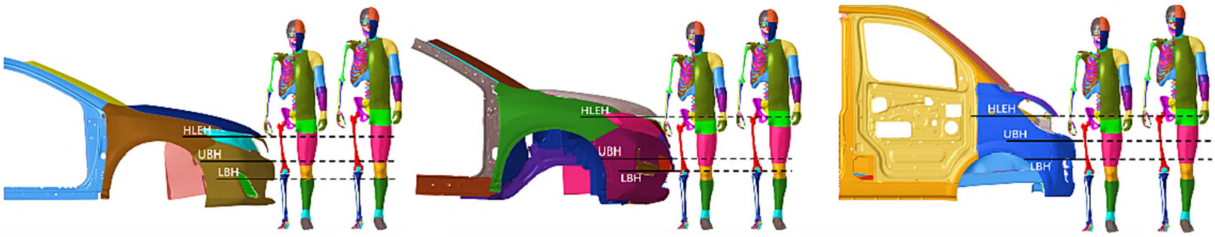


FIGURE 3
Comparison of vehicle structure and relative position of human body (L: sedan, Center: SUV, R: MPV).

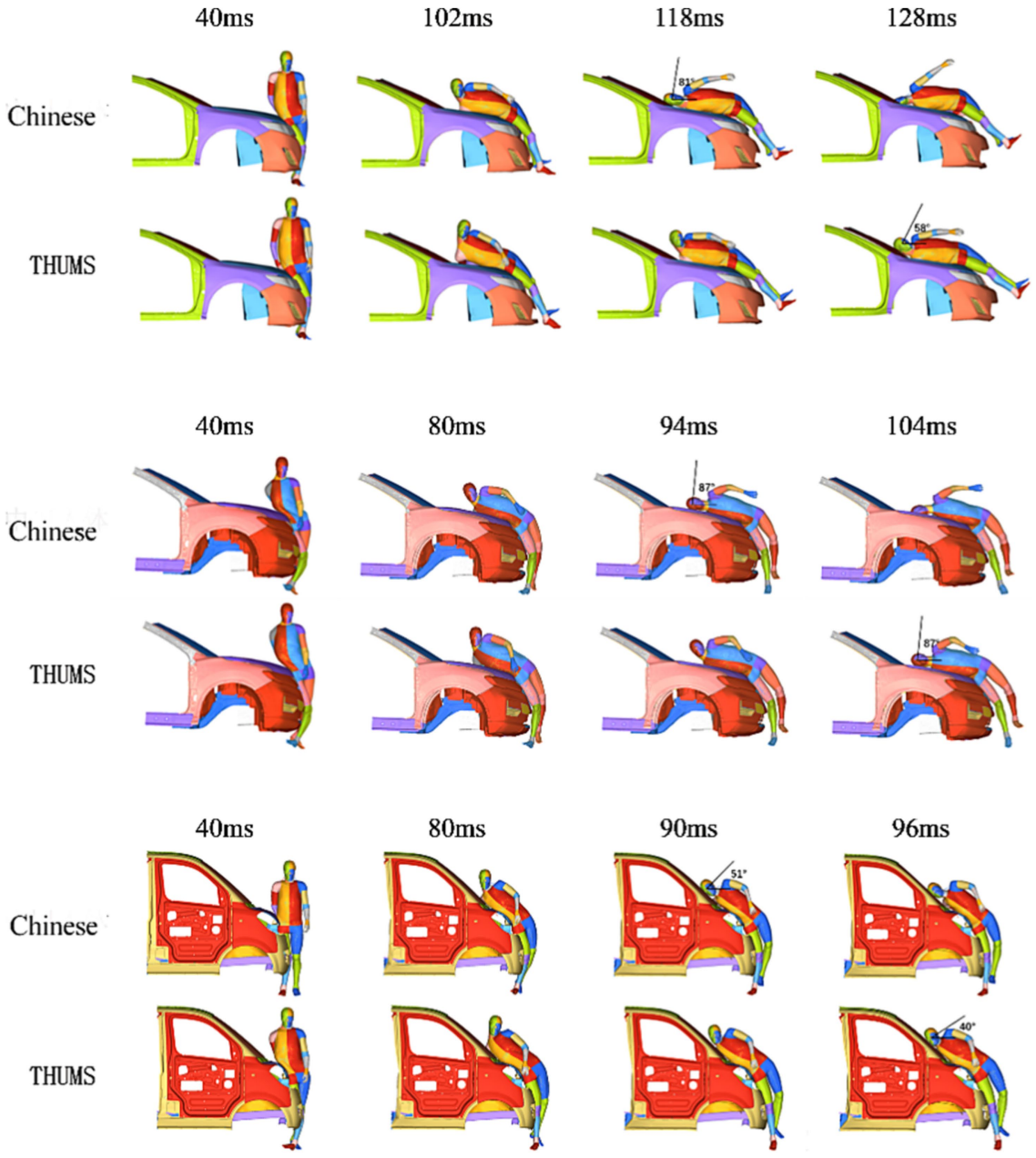


FIGURE 4
Comparison of kinematics responses of mannequins in different countries during side collision.

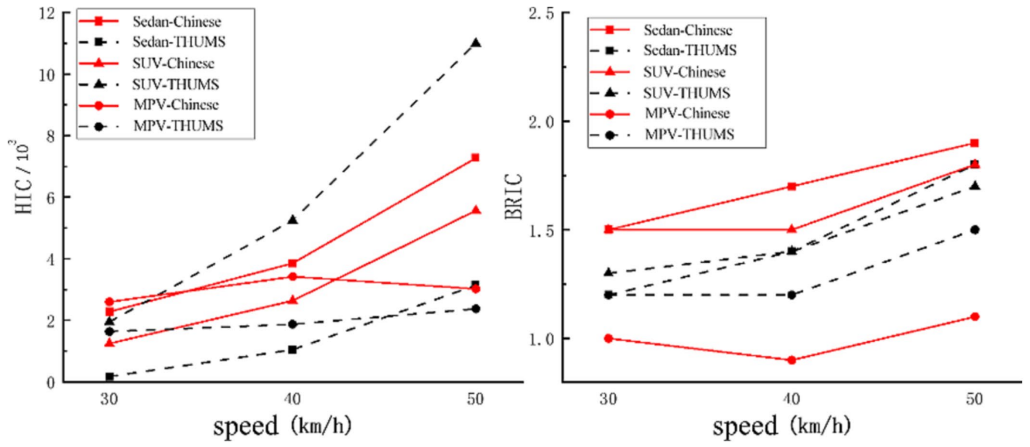


FIGURE 5
Comparison of HIC and BRIC of mannequin heads at different speeds.

TABLE 3 Comparison of head injury response peaks (vehicle speed 40 km/h).

	Human model	Sedan	SUV	MPV	Reference number
Head integrated acceleration (g)	Chinese human body	196	185	211	/
	THUMS	119	254	139	
HIC_{15}	Chinese human body	3,854	2,639	3,419	700
	THUMS	1,046	5,245	1870	
BRIC	Chinese human body	1.7	1.5	0.9	1
	THUMS	1.4	1.4	1.2	
Maximum equivalent stress on the skull (Mpa)	Chinese human body	146	107	125	65
	THUMS	104	122	150	
Brain tissue MPS	Chinese human body	0.86	0.83	0.82	0.3
	THUMS	0.7	0.8	0.99	
Brain tissue CSDM	Chinese human body	0.25	0.67	0.39	0.54
	THUMS	0.08	0.61	0.35	

maximum stress on the Chinese mannequin skull was 125 Mpa, which appeared in the parietal bone, and the maximum stress on the THUMS model skull was 150 Mpa, which appeared in the temporal bone.

The maximum principal strain on the brain of the Chinese mannequin was 0.86, and the maximum principal strain on the brain of the THUMS model was 0.70 when the sedan model crashed. When the SUV model and mannequins collided, the maximum principal strain on the Chinese mannequin brain was 0.83, and the maximum principal strain on the THUMS model brain was 0.80. The maximum principal strain on the brain of the Chinese mannequin was 0.82, and the maximum principal strain on the brain of the THUMS model was 0.99 during the collision of the MPV model.

Discussion

In the 2021 version of the C-NCAP management rules, the pedestrian protection test specifies that the impact speed of the adult headform impactor is 40 km/h and the impact angle is 60 °(windshield) (27). The present paper simulated the kinematics response of the head when a sedan impacted two mannequins at a speed of 40 km/h (Figure 8). When the head came into contact with the vehicle, the speed of the THUMS head center of gravity was 39.9 km/h, and the angle was 58°. The speed of the Chinese head center of gravity was 40.4 km/h, and the angle was 81°, much higher than the 60° set in the test. The larger impact angle of the Chinese human head also led to higher *Z*-axis acceleration, resulting in higher HIC values when impacted by the rear structure of the hood. Therefore, when conducting pedestrian protection head impact tests targeting the Chinese human body, it is possible to consider adjusting the head impact angle, especially at the transition area between the windshield and the rear end of the hood.

The HIC value depends on the head impact speed, the location of the head being impacted, and the contact area with the vehicle body. When the sedan model collided with the mannequins at a speed of 40 km/h, the Chinese human head collided with the transition area between the engine hood and windshield, while the THUMS head collided with the windshield. The difference in stiffness between the two areas resulted in a difference in HIC values.

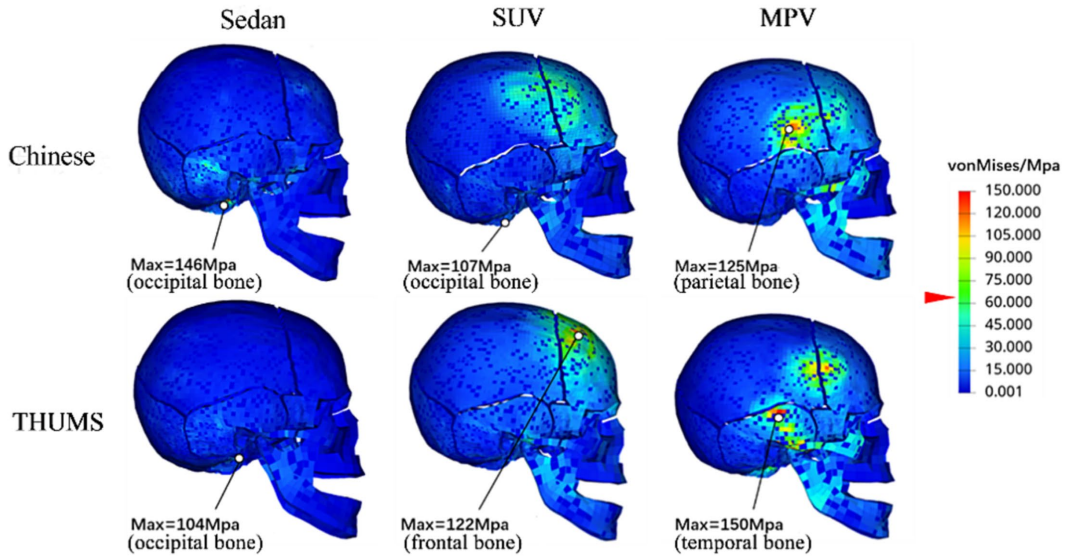


FIGURE 6
Cloud diagram of equivalent force on the collision side of the skull.

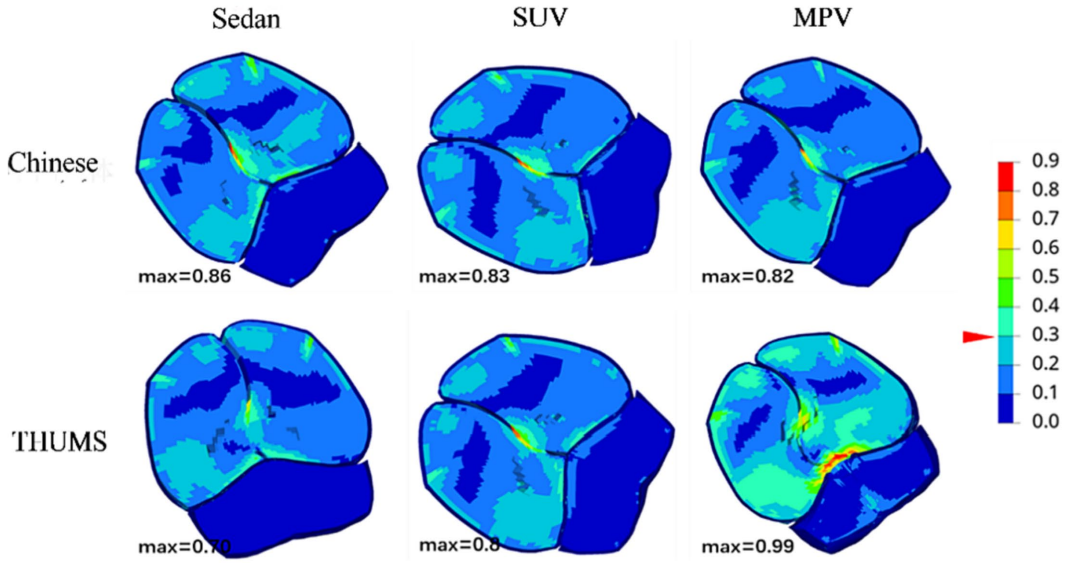


FIGURE 7
Principal strain cloud map of the central cross-section of the brain.

The collision situation of the SUV model was the same, with the THUMS head colliding with the rear end of the engine hood. The collision position of the Chinese human head was more forward, with lower structural stiffness, resulting in a lower HIC value. During the MPV collision, the head of the two mannequins collided with the windshield. However, due to the different impact angles, the initial impact parts of the head of the two mannequins were significantly different. The head of the Chinese human body collided with the vehicle first, and the face of the THUMS collided with the vehicle first, which led to a higher HIC of the head of the Chinese human body, and also led to a difference in the damaged parts of the skull of the two human bodies. A previous study (28) also proved that there is a significant positive correlation between pedestrian head collision angle and head linear acceleration.

The collision impact force with vehicle structural components is the main cause of skull fractures. According to the literature (29, 30), the fracture stress of the cortical bone of the skull is between 48 and 128 Mpa, and the fracture stress of the dense bone is between 32 and 74 Mpa. Wood et al. determined that the fracture stress of the skull is approximately 65 Mpa. Using 65 Mpa as the threshold, when the sedan collided with the mannequins, the occipital and sphenoid bones of both types of human bodies fractured. When the SUV collided, fractures occurred in the parietal, frontal, occipital, and sphenoid bones of both types of human bodies. When the MPV collided, all the

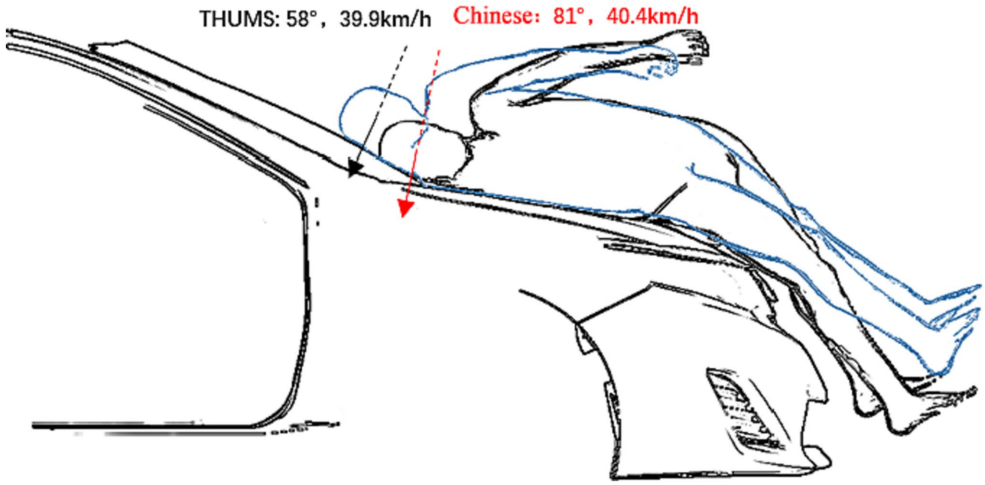


FIGURE 8
Comparison of head impact velocity and angle between two mannequins.

skulls on the impact side were fractured, and the maximum stress in the Chinese human body was concentrated in the parietal bone, while the maximum stress in the THUMS was concentrated in the temporal bone. We then calculated the fracture area of the skull. When the sedan collided, the fracture area in the Chinese human skull was 1,139 mm^2, and in the THUMS it was 197 mm^2. When the SUV collided, the fracture area in the Chinese human skull was 1,690 mm^2, and in the THUMS it was 3,629 mm^2. When the MPV collided, the fracture area in the Chinese human skull was 944 mm^2, and in the THUMS it was 1726 mm^2.

From this, it can be seen that, both in terms of peak stress and fracture area, the sedan model led to more severe damage to the Chinese human skull, while the SUV and MPV models led to more severe damage to the THUMS skull. It is worth noting that although the MPV model caused more severe damage to the skull of THUMS, the HIC value of THUMS was lower than that of the Chinese human body because it is related to the head impact angle mentioned above. This phenomenon further demonstrates the important role of head impact angle in skull injury analysis and also suggests the limitations of headform impactors in simulating complex skull structures in humans.

By measuring and comparing the velocities and accelerations of two different parts of the human body, it was inferred that the magnitude of head angular velocity was mainly related to chest acceleration. When the shoulders of the mannequin came into contact with the engine hood, the chest speed decreased rapidly. The difference between the head speed and the chest speed led to the rapid increase of the head angular speed. Therefore, when the shoulders came into contact with the structural parts with greater stiffness, the chest decelerated faster and the head BRIC was larger. The inevitable drawback of this study is that the HIC criterion based on linear composite acceleration lacks consideration for other brain injury load conditions. For example, when the head is subjected to inertial loads in the acceleration field, relative motion between the skull and brain will occur, resulting in high shear strain and strain rate that can lead to brain tissue damage, and this type of brain damage is likely to occur without skull fractures. The 2018 version of the US New Car Evaluation Regulations (US-NCAP2018) requires that the BRIC value be calculated from the angular velocities in the three different directions of the head. According to the study by Thakhonts et al. (31), when the BRIC is 1, the probability of brain AIS4+ injury is 50%, and when the BRIC is 1.5, the probability of brain AIS4+ injury reaches 80%. According to this conclusion, the probability of AIS4+ injury in Chinese human bodies during sedan and SUV collisions exceeds 80%, with a higher probability of brain damage. In contrast, during MPV collisions, the THUMS model's AIS4 + damage probability exceeded 50%, resulting in a higher probability of brain damage. The study conducted by Watanabe et al. (3) also reached similar conclusions.

The study of Bain et al. (32) showed that brain tissue damage and contusion occur when the main strain of the white matter exceeds 30%. According to this standard, all three vehicle models can cause damage to brain tissue when driving at a speed of 40 km/h. For the prediction of diffuse axonal injury (DAI), Thakhonts et al. (31) proposed the cumulative strain damage measurement (CSDM) as an evaluation metric, which assumes that DAI occurs when a principal strain of over 0.25 occurs in 49% of the entire brain region. As shown in Table 3, the head injury volume of the Chinese human body during collisions of the three vehicle models was greater than that of THUMS, and during SUV collisions, both types of human head injuries occurred. In addition, Thakhonts also proposed that there is a 50% probability of AIS4 + level severe brain injury occurring when MPS equals 0.89, so when MPV collides with THUMS, DAI may also occur in the head.

The research results suggest that the peak principal strain of brain tissue occurs 1–5 ms before the collision between the head and the vehicle. At this time, the angular velocity of the brain is accelerating and approaching the peak, indicating that in this study, the MPS of brain tissue is mainly related to the inertial load during the rotation process. When the head collides with the vehicle, the MPS decreases, but the volume of brain tissue with strain exceeding 0.25 sharply increases, indicating that the CSDM value is affected by the combined

impact force and rotational inertia load. This not only explains the difference in the comparison of MPS and CSDM values when the MPV model collided with the two types of human bodies but also indicates that when analyzing the strain of pedestrian brain tissue, these two indicators should be considered comprehensively.

Mueller (33) counted the HIC and BRIC values of the Hybrid III dummy in 128 crash tests and found that there was no correlation between HIC and BRIC. They assessed the risk of head injury from different angles and concluded that the two criteria should be used together. Takcounts et al. also provided a similar explanation. In the present article, it could also be observed that when using HIC and BRIC values to compare two types of human head injuries, the comparison results may not be consistent. For example, when the SUV model collided with the two types of human bodies, the HIC value of the Chinese human body was lower than THUMS, but the BRIC value was higher. Based on the injury response of the skull and brain tissue, it could be concluded that the degree of skull injury in Chinese humans was lower than that in THUMS, but the brain tissue injury was more severe. Therefore, it is necessary to combine these two indicators when analyzing pedestrian head injury.

Overall, at a collision speed of 40 km/h, the Chinese human body suffers more severe skull damage in sedan collisions and more severe brain damage in sedan and SUV collisions, whereas THUMS suffers more severe skull damage during SUV and MPV collisions, and more severe brain damage during MPV collisions. When the C-NCAP pedestrian protection testing procedure based on THUMS is applied, it may not provide the best protection for Chinese pedestrians. It is recommended that the testing procedure be improved by combining collision damage mechanisms and the physical characteristics of Chinese pedestrians.

In this research, a comparison was made between the differences in head and brain injuries resulting from vehicle collisions among the 50th percentile adult males in China and the United States. When factors such as pedestrian height, weight, age, initial collision posture, and other variables vary, the outcomes of injuries can vary significantly. Therefore, this research cannot account for variations in pedestrian injuries between the two countries in all circumstances. Furthermore, this study compared differences in bodily injuries between pedestrians of the two countries using the same tolerance threshold. In the future, it is essential to take into account a broader range of body types and conduct more in-depth research based on variations in individual tolerance thresholds.

Conclusion

This article constructs a finite element model of the Chinese 50th percentile human body and achieves the required biological fidelity. Through finite element simulation, the head dynamics and injury response of the Chinese mannequin and the THUMS model in the collision of sedans, SUVs, and MPVs were compared. It was found that the collision time, collision position, invasion speed, and angle of the Chinese mannequin head were significantly different from those of the THUMS. When a sedan collided, the skull damage to the Chinese human body was more severe, and when a sedan or SUV collided, the brain damage to the Chinese human body was more severe. The existing C-NCAP pedestrian protection testing regulations may not provide the best protection for the Chinese human body. It is recommended that testing regulations be improved by combining collision damage mechanisms and the physical characteristics of Chinese pedestrians.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

LY: Writing – original draft, Writing – review & editing, Investigation. CL: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. XZ: Data curation, Methodology, Writing – original draft. DZ: Formal Analysis, Writing – original draft. XL: Methodology, Validation, Writing – original draft. XK: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Resources, Visualization.

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Conflict of interest

XZ was employed by Shanghai Motor Vehicle Inspection Certification and Tech Innovation Center Co., Ltd. DZ and XL were employed by Geely Automobile Research Institute (Ningbo) Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1296902/full#supplementary-material

References

1. Hu Y, Liu X. *Automotive Pedestrian Protection Development Technology.* Beijing: Tsinghua University Press (2014).

2. Ministry of Road Transport and Highways (2019). Traffic accident statistics annual report. Institute for Traffic Accident Research and Data Analysis.

3. Watanabe R, Katsuhara T, Miyazaki H, Kitagawa Y, Yasuki T. Research of the relationship of pedestrian injury to collision speed, car-type, impact location and pedestrian sizes using human FE model (THUMS Version 4). *Stapp Car Crash J.* (2012) 56:269. doi: 10.3390/nu4101504

4. Tamura A., Nakahira Y., Iwamoto M., Watanabe I., Miki K., Hayashi S., et al. (2006). "The influence of the traction force due to inertia of the brain mass on traumatic brain injury during SUV-to-pedestrian impact." IRCOBI. Washington DC, United States.

5. Yang JK, Xu W, Xiao Z, Li F. A study on head injury BIOMECHNICS in CAR-to-pedestrian collisions using human body models. *J Biomech.* (2007) 40:S87. doi: 10.1016/S0021-9290(07)70084-2

6. Wei H (2019). Study on the influence of neck muscle activation on head-neck response in pedestrian collision accidents. Changsha, Hunan University.

7. Bougourd J, Treleaven P (2010). UK national sizing survey–size UK. *International Conference on 3d Body Scanning Technologies*. 19–20. doi: 10.15221/10.327

8. Robinette KM, Blackwell S, Daanen H, Boehmer M, Fleming S. (2002). Civilian American and European surface anthropometry resource (CAESAR), final report, volume I: Summary. Sytronics Inc Dayton Oh. I, 1~66.

9. China National Institute of Standardization Research. (2020) The Latest Survey of Basic Ergonomic Parameters for Chinese Adults Has Been Completed [EB/OL].[2022-03-15]. Available at: https://www.cnis.ac.cn/ynbm/jcbzhyjs/kydt/202010/t20201028_50419.htm

10. Shigeta K, Kitagawa Y, Yasuki T. Development of next generation human body FE model capable of organ injury prediction. *Proceedings of the 21st annual enhanced safety of vehicles*. (2009) 15–18.

11. Iwamoto M., Kisanuki Y., Watanabe I., Furusu K, Miki K, Hasegawa J (2002). Development of a finite element model of the total human model for safety (THUMS) and application to injury reconstruction. *Proceedings of the international IRCOBI Conference.* 18–20.

12. Yoganandan N, Pintar FA, Sances A Jr, Walsh PR, Ewing CL, Thomas DJ, et al. Biomechanics of skull fracture. *J Neurotrauma*. (1995) 12:659–68. doi: 10.1089/neu.1995.12.659

13. Hardy WN, Foster CD, Mason MJ, Yang KH, King AI, Tashman S. Investigation of head injury mechanisms using neutral density technology and high-speed biplanar X-ray. *Stapp Car Crash J.* (2001) 45:337–68. doi: 10.4271/2001-22-0016

14. Kleiven S, Hardy WN. Correlation of an FE model of the human head with local brain motion–consequences for injury prediction. *Stapp Car Crash J.* (2002) 46:123–44.

15. Shaw JMHR, McFadden JD, Donnelly BR, Bolte JH. Oblique and lateral impact response of the PMHS thorax. *Stapp Car Crash J.* (2006) 50:147–67. doi: 10.4271/2006-22-0007

16. Kajzer J, Schroeder G, Ishikawa H. Shearing and bending effects at the knee joint at high speed lateral loading. *SAE Trans*. (1997) 106:3682–96.

17. Kajzer J, Matsui Y, Ishikawa H. Shearing and bending effects at the knee joint at low speed lateral loading. *SAE Trans*. (1999) 107:1159–70.

18. Merz H J. (1984). A procedure for normalizing impact response data, SAE Paper No. 840884. 351–358.

19. Viano DC. Biomechanical responses and injuries in blunt lateral impact. *SAE Trans.* (1989) 98:1690–719.

20. Lobdell T E, Kroell C K, Schneider DC, Hering W. E., Nahum A. M. (1973). Impact response of the human thorax. Human impact response: Measurement and simulation. 201–245.

21. Dejun B (2011). Research on vehicle-to-pedestrian traffic accident speed reproduction. Harbin Institute of Technology, Harbin.

22. Yuan Q, Li Y, Mei B. Comparative study on characteristic parameters of Car collision with pedestrians and bicycle riders. *J Traffic Transport Eng*. (2005) 3:92–9. doi: 10.3969/j.issn.1672-4747.2005.03.014

23. Wu G. Statistics and collision analysis of urban pedestrian traffic accidents. *Sci Technol Info*. (2012) 24:473–6. doi: 10.3969/j.issn.1001-9960.2012.24.423

24. Khan AM, Yonten K, Eskandarian A, Arispe E, Summers S. (2015) Development and Validation of Finite Element Models of Mid-Size Sedan Including Interiors for Crashworthiness Simulations.Transportation Research Board Meeting. No. 15-4440.

25. Reichert R, Mahadevaiah U, Fuchs L, Kan CD. (2022) Development of a 2020 SUV vehicle FE model. *16th LSDYNA Forum 2022*. Bamberg, Germany. Available at: https://www.ccsa.gmu.edu/models

26. Honghu L, Long X, Aiguo C, Xue C. Lightweight Design of a Miniature Car Body Based on stiffness and modal analysis. *Automot Eng.* (2011) 3:6. doi: 10.3969/j.issn.1000-3703.2011.03.004

27. CATARC Europe (2021). China Automotive Technology Research Center Co., Ltd. (Tianjin), C-NCAP Management Rules (2027 Edition).

28. Xiaoqiang H (2022). Simulation of dummy-windshield impact and head injury research. Guangdong: Guangdong University of Technology.

29. McElhaney JH, Fogle JL, Melvin JW, Haynes RR, Roberts VL, Alem NM. Mechanical properties of cranial bone. *J Biomech*. (1970) 3:495–511. doi: 10.1016/0021-9290(70)90059-X

30. Wood JW. Dynamic response of human cranial bone. *J Biomech*. (1971) 4:1–12. doi: 10.1016/0021-9290(71)90010-8

31. Takhounts EG, Craig MJ, Moorhouse K, McFadden J, Hasija V (2013). Development of brain injury criteria (BrIC). SAE Technical Paper. 22–0010.

32. Bain AC, Meaney DF. Tissue-level thresholds for axonal damage in an experimental model of central nervous system white matter injury. *J Biomech Eng.* (2000) 122:615–22. doi: 10.1115/1.1324667

33. Mueller B, Macalister A, Nolan J, Zuby D. (2015). "Comparison of HIC and BrIC head injury risk in IIHS frontal crash tests to real-world head injuries" in *Proceedings of the 24th International Technical Conference on the Enhanced Safety of Vehicles*. 1–18.

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The bibliometric and altmetric analysis of chronic traumatic encephalopathy research: how great is the impact?

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Background: The study of chronic traumatic encephalopathy (CTE) has received great attention from academia and the general public. This study aims to analyze the research productivity on CTE and investigate the most discussed articles in academia and the general public by conducting bibliometric and altmetric analyses.

Methods: Data of articles were obtained from the Web of Science Core Databases and Altmetric Explore. VOSviewer and CiteSpace software were used to analyze and visualize the articles. The correlation between Altmetric attention scores (AAS) and citation counts were assessed by Spearman correlation coefficient.

Results: 788 publications of CTE were eventually gathered and analyzed, and 100 articles with highest citation counts (Top-cited) and 100 articles with highest AASs (Top-AAS) were then identified. The keywords density map showed both the general public and the scientists were particularly interested in the risk factors and pathology of CTE, and scientists were interested in the causes and characteristics of neurodegenerative diseases while the public became increasingly concerned about the detection and prevention of CTE. By examining the shared characteristics of the 44 articles (High-High articles) that overlapped between Top-cited and Top-AAS articles, we identified certain traits that may potentially contribute to their high citation rates and high AASs. Besides, significant positive correlations with varied strength between AAS and citation were observed in the 788 articles, Top-cited, Top-AAS and High-High datasets.

Conclusion: This study is the first to link bibliometric and altmetric analyses for CTE publications, which may provide deeper understanding of the attention of the scientists and the general public pay to the study of CTE, and offer some guidance and inspiration for future CTE in the selection of research topics and directions.

KEYWORDS

chronic traumatic encephalopathy, altmetric attention score, bibliometric analysis, comparation, twitter

Introduction

Chronic traumatic encephalopathy (CTE) is a progressive tauopathy that occurs due to repetitive mild traumatic brain injury (1). Over 93 years ago, Martland originally described the clinical aspects of a progressive neurological decline as "punch drunk," which occurred after repetitive brain trauma in boxers (2). With the development of research, "chronic traumatic encephalopathy" was widely used to describe the disease. Later studies reported that CTE was unrestricted to boxing but also happened in various contact sports, including football, wrestling, rugby, hockey, lacrosse, soccer, and skiing (1). More than that, CTE has been diagnosed in military veterans with combat exposure and others who have suffered frequent head impacts (3–5). Although some reports suggest that degenerative brain disease is almost unavoidable for athletes participating in certain sports, a cause-and-effect relationship between exposure to contact sports and CTE has not been demonstrated (6). Yet, the actual prevalence of CTE is unknown (7). There are currently no definitive criteria for a diagnosis of CTE during life, and identifying CTE in a living individual is still challenging. The disease can only be definitively diagnosed through post-mortem examination of the brain tissue (8). In 2014, based on the literature of the clinical manifestations of CTE from 202 published cases, research diagnostic criteria for traumatic encephalopathy syndrome (TES) were proposed to diagnose CTE pathology in life (9). These criteria were used as a starting point and initial organizing structure for the development of following consensus criteria- NINDS Consensus Diagnostic Criteria for TES (9). And these criteria would be an invaluable tool to enhance the ability to diagnose and manage TES/CTE in individuals and possibly mitigate the associated consequences. Meanwhile, clinical symptoms of CTE can be nonspecific, and there may be overlap with other neurodegenerative diseases (10). In recent years, significant progress and achievements have been made in the field of CTE research, such as the development of advanced imaging techniques (11), identification of specific protein biomarkers (12), underlying pathogenesis of CTE (13), and potential therapeutic targets and interventions (14). In addition to the attention received in the research field, the term CTE has gained significant public attention due to intense media coverage. It has even been the subject of numerous documentaries and a Hollywood movie. Since CTE poses a threat to a significant part of the population and attracts the attention of scientists and the general public, it is important to analyze the dissemination and influence of CTE-related research in academia and the general public.

Bibliometrics is a traditional useful tool for evaluating the productivity, impact, and research trends in a certain field. From a scientific perspective, bibliometrics for determining the value of scientific research centers on the number of times the article is cited and the impact factor of the journal in which the article is published (15, 16). Besides, with the emergence and development of the internet and social media, altmetrics, shorter for alternative metrics, are increasingly utilized as nontraditional metrics of scholarly impact by a weighted calculation of the attention an article receives online (17). Data resources for altmetrics include Twitter, Facebook, blogs, news outlets, Wikipedia, Google, Weibo, Reddit, and other online platforms such as YouTube (18). Altmetric Explorer (Altmetric LLP, London, United Kingdom) generates a weighted score, known as Altmetric Attention Score (AAS). AAS tracks the online presence of articles by measuring and compiling the mentions an article receives across various social media outlets. Besides, AAS allows for continuous updating, and reflects an article's online attention trends. In recent years, CTE has garnered increased public attention. The most-read article with an extremely AAS published in *The Journal of the American Medical Association (JAMA)* in 2017 reported that 110 of 111 (99%) former football players were suspected of having CTE (19). The article caused extensive controversy and sustained attention and discussion in society until now. Thus, altmetric analysis of CTE productions can help us understand how CTE research is being received and utilized by the general public, and provide evidence of the broader impact of CTE research beyond traditional bibliometric metrics.

Studies have combined bibliometric and altmetric analyses to conduct in-depth researches in some research areas, including osteoporosis, nuclear medicine, reproductive biology, obstetrics and gynecology, and urology (20–24). There were some bibliometric or altmetric studies on CTE in the literature (25–27). However, to the best of our knowledge, this is the first study that combines bibliometric with altmetric analysis about CTE. In this study, we aim to address the following issues: 1. identify the characteristics of total CTE article; 2. examine the traits and commonalities/differences between articles with the highest citation counts and articles with the highest AASs; 3. determine if there is any overlap between articles with the highest citation counts and articles with the highest AASs; 4. conduct an analysis of these overlapped articles. This study may be beneficial to the publication of papers by investigators and the design for the future research of CTE.

Materials and methods

Data sources

The data for measurement and statistical analysis were screened from the Web of Science Core Collection (WoSCC) and Altmetric Explorer[1] on March 2023. We chose WoSCC because it collects scientific publications with the most significant impact and is used as the main criterion in academic decision making. Altmetric Explorer was used to obtain AAS data of the literature from WoSCC. Approval by institutional review boards was not required as the analysis was based on publicly accessible data. This cross-sectional altmetric and bibliometric study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies (28).

Search strategy

The search strategy in the WoSCC database were as follows:
#1 TI = "chronic traumatic encephalopathy."
#2 AB = "chronic traumatic encephalopathy."
#3 AK = "chronic traumatic encephalopathy."
#4 #1 OR #2 OR #3.

1 https://www.altmetric.com/

Inclusion and exclusion criteria

Inclusion criteria Document type: articles and reviews; Language: English. The results were arranged using a link on WoSCC database system "sort-by Citation-highest first." Then, three independent investigators reviewed the titles and abstracts and deleted studies that were not associated with CTE. Any disagreements were resolved through discussion, and the input of an independent colleague would be sought where consensus could not be reached. The 839 records were selected and exported to an excel format. The DOI or PubMed identification number of articles were entered into the advanced search tool of Altmetric Explorer.

Exclusion criteria Articles without any AAS data were excluded. Eventually records for 788 articles that received altmetric activities were retrieved (Figure 1).

Analysis of articles

Bibliometric data of 788 articles were downloaded from the WoSCC, and altmetric data of 788 articles were downloaded from Altmetric Explorer on March 2023. The analyses were performed using IBM SPSS, version 24 (Statistical Package for Social Sciences, Chicago, IL). For bibliometric data, we recorded title, study type, topic of the study, authors, organizations, publication year, citation number, keywords, journal name and impact factor. For altmetric data of 788 articles, we recorded the AASs and the number of mentions on Twitter, news outlets, blog posts, policy mentions, patent mentions, peer mentions, Facebook, and Wikipedia for each article. To provide insight into the characteristics of CTE research that with high citation rates and high AASs, the 100 articles with highest citation counts (Top-cited) and the 100 articles with highest AASs (Top-AAS) were identified for further research. The Spearman correlation coefficient was used to assess the correlation between AASs and citation numbers, and was interpreted according to r-level as follows: <0.19 (very weak), 0.2–0.39 (weak), 0.4–0.59 (moderate), 0.6–0.79 (strong), and > 0.8 (very strong). $p < 0.01$ was considered statistically significant.

Data visualization

In this study, VOSviewer (version 1.6.18) and CiteSpace (version 6.1.R2) were used for data visualization of Top-cited and Top-AAS articles. The keyword density visualization map was plotted by utilizing VOSviewer to identify the study subjects in a certain field and explore the research hotspots (29). The timeline review of keywords was exported by CiteSpace to show the chronological distribution and historical evolvement of knowledge domains (30).

Results

Characteristics of total 788 articles

Based on the study's strategic flowchart, we eventually gathered 788 publications, and the related data were downloaded from WoSCC and Altmetric Explorer. As shown in Table 1, among the 788 articles, 63

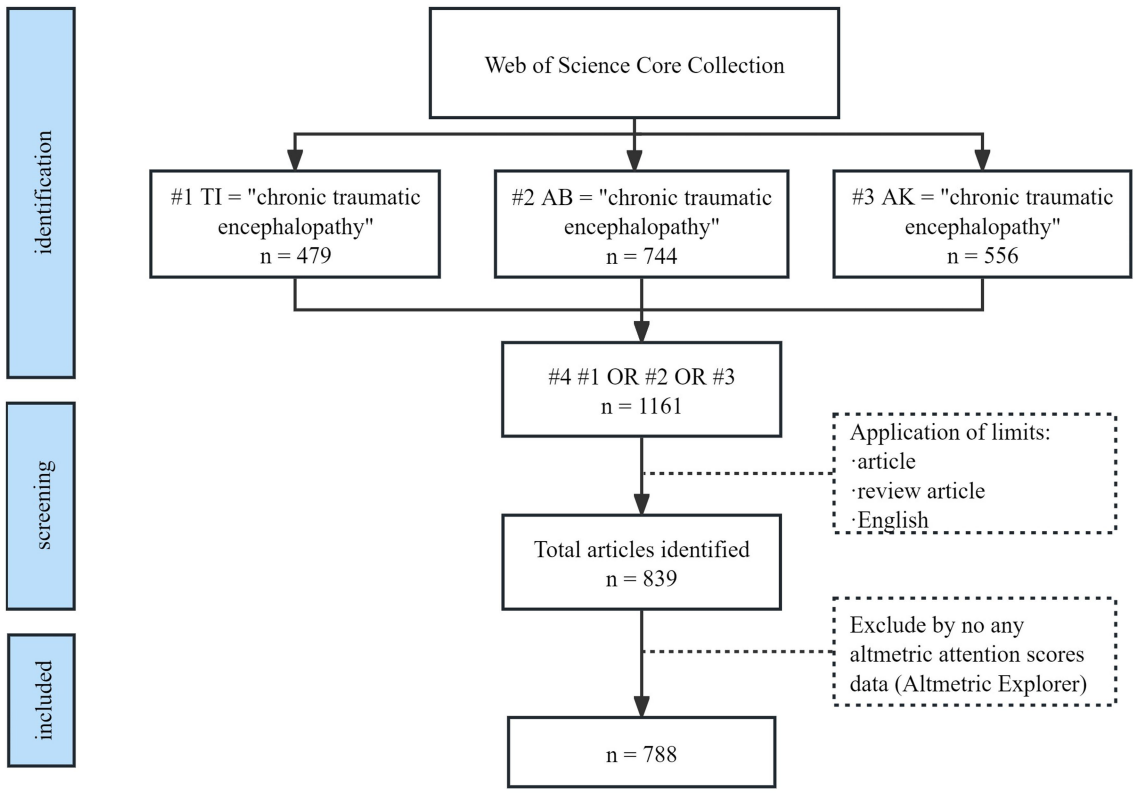

FIGURE 1
Flowchart detailing the paper collection and screening process.

TABLE 1 Characteristics of total 788 articles.

Characteristics		Results
Citation	Citation ≥1,000	$n = 3$
	Citation 500–999	$n = 5$
	Citation 1–499	$n = 717$
	Citation 0	$n = 63$
	Average citation	48.85
AAS	AAS ≥1,000	$n = 5$
	AAS 500–999	$n = 12$
	AAS 1–499	$n = 741$
	AAS 0	$n = 30$
	Average AAS	55.77
Correlation of AASs and citation numbers		$r = 0.406^{**}$, $p < 0.01$
AAS source	Twitter	24.74
	News	6.40
	Blog	0.61
	Facebook	0.97
	Wiki	0.26
	Google	0.18
Open access		$n = 262$

articles were cited 0 times, 717 were cited 1 to 499 times, 5 were cited 500 to 999 times, and 3 were cited ≥1,000 times. There were 30 articles with AASs of 0, 741 articles with AASs between 1 and 499, 12 articles with AASs between 500 to 999, and 5 articles with AASs of ≥1,000. There was a moderate correlation between AASs and citation numbers ($r = 0.406^{**}$, $p < 0.01$). We then analyzed the average number of online mentions per source for the 788 articles included in the study. Each online source in altmetrics is assigned a weight, such as 8 for every mention in a news article (Supplementary Table S1), and each publication is assigned every source score. The results showed that for the 788 articles the average score of Twitter was 24.74 and the average score of News was 6.40, which were far higher than other sources, indicating that Twitter and News outlets were the principal drivers of attention (Table 1). To provide a more detailed analysis of the AASs, we tracked the sources of AASs for 788 articles over time. Figure 2 showed the temporal evolution of mentions for all 788 research outputs between 2009 to 2023. The highest point of the waterfall chart, representing the peak of attention, manifested on Twitter in July 2017 with 1,311 mentions. The peak of News also appeared in July 2017 with 364 mentions. This surge in attention was not arbitrary, but directly correlated with the publication of a groundbreaking article by Dr. McKee et al. titled "Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football," published in *JAMA* (19). This work presented the largest CTE case series until 2017, revealing the presence of CTE in all but one of the 111 (99%) participants who were former National Football League players.

Characteristics of the Top-cited and Top-AAS articles

We also conducted a detailed analysis of the citation counts, AASs, study designs, and open access status of the Top-cited and Top-AAS articles (Table 2). Among the Top-cited articles, 92 were cited 90 to 499 times, 5 were cited 500 to 999 times, and 3 were cited ≥1,000 times. Average citation of Top-cited articles was 244.88. There were 57 articles with AASs of 0–79, 34 articles with AASs between 80 and 499, 4 articles with AASs between 500 to 999, and 5 articles with AASs of ≥1,000. Average AAS of Top-cited articles was 225.49. Among the Top-AAS articles, 56 were cited 1 to 89 times, 36 were cited 90 to 499 times, 5 were cited 500 to 999 times, and 3 were cited ≥1,000 times. Average citation of Top-AAS articles was 157.57. There were 83 articles with AASs between 80 and 499, 12 articles with AASs between 500 to 999, and 5 articles with AASs of ≥1,000. Average AAS of Top-AAS articles was 341.6. A weak correlation was found between correlation of AASs and citation numbers in Top-cited articles ($r = 0.36^{**}$, $p < 0.01$) and in Top-AAS articles ($r = 0.247^{*}$, $p < 0.05$). As for the study design, nearly half of Top-cited articles were review ($n = 47$), and a quarter of Top-cited articles were basic study ($n = 25$), whereas nearly half of Top-AAS articles were observational study ($n = 47$), including case control ($n = 17$), case report ($n = 8$), case series ($n = 6$), cohort study ($n = 13$), cross-sectional ($n = 3$). Besides, Top-cited ($n = 82$) and Top-AAS ($n = 89$) articles were both more likely to be open access.

Research hot topics of CTE

We separately plotted in Figures 3A,B the keyword density visualization map of the Top-cited and Top-AAS articles utilizing VOSviewer, and detailed keywords lists were presented in Table 3. Density views are especially useful for understanding the overall structure of a map and drawing attention to the most important areas on it (29). Each node in the keyword density visualization plot had a color that relied on the density of items at that node. The keywords in the red area appeared more recurrent, indicating the keywords were the most frequently occurring hot topics. We found that "chronic traumatic encephalopathy," "Alzheimer's disease," "traumatic brain injury," "concussion" and "brain-injury" were the hot topics both appeared in the Top-cited map and Top-AAS map. In addition to the hot keywords that both appeared in Top-cited map and Top-AAS map, we also found that some keywords "amyloid precursor protein," "cerebrospinal-fluid diffuse," "axonal injury" and "microglial activation" only appeared in Top-cited map, and "diagnosis," "criteria" and "neuropathologic assessment" only appeared in Top-AAS map.

Knowledge evolution of CTE

In the CiteSpace timeline view, we could clearly see the evolution of each cluster over time. Each node in the network can be clustered together according to its interconnectivity to form different clusters, with each cluster representing a different professional or disciplinary concept (30). As shown in Figures 4A,B, the cluster and timeline views of the Top-cited and Top-AAS articles were presented, and clusters information were listed in Supplementary Table S2. The active time of each cluster on the timeline reflected the attention given to the research topic in different periods. The modularity value and the mean silhouette score were 0.614 (>0.3), 0.843 (>0.5) in Top-cited and 0.521 (>0.3), 0.813 (>0.5) in Top-AAS, indicating that the structures of clusters were significant and the clusters were efficient and convincing

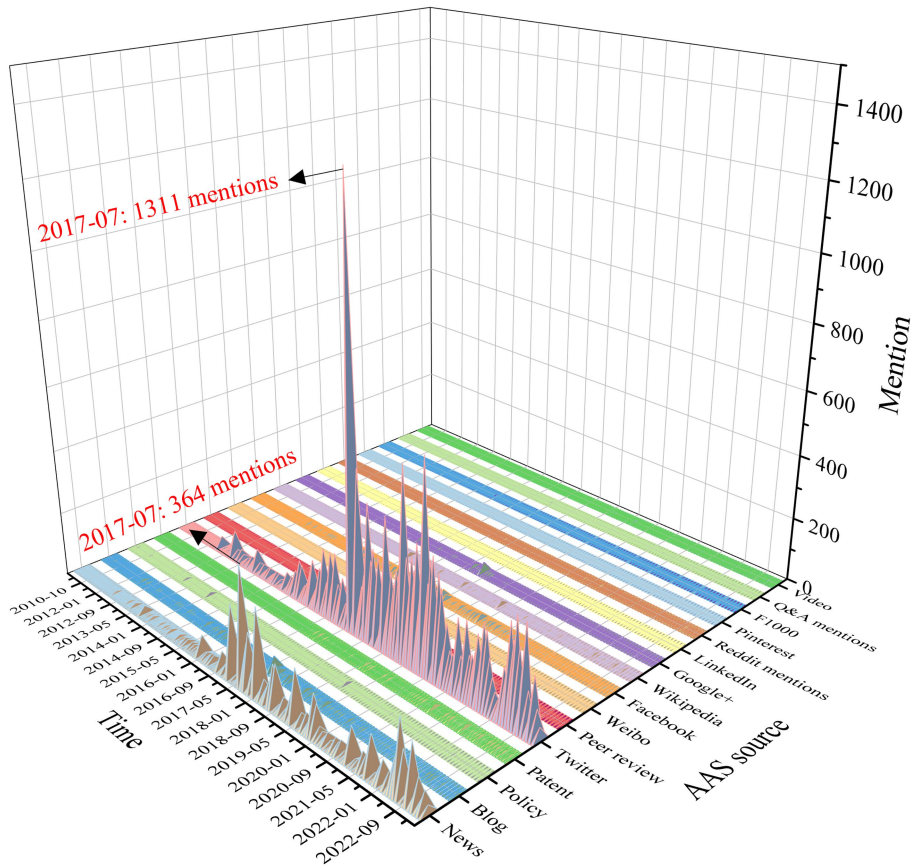

FIGURE 2
Mentions over time of each AAS online source of 788 research outputs. The peak of News and Twitter appeared in July 2017 with 364 and 1,311 mentions.

(30). In timeline view of Top-cited, there was a total of 9 clusters. #0 concussion, #1 dementia pugilistica, #3 motor neuron disease and #4 brain injury had been active since 1995, whereas #2 cerebrospinal fluid, #5 neurodegenerative disorders, #8 hypercapnia and #9 bbb began to receive attention in approximately 2010. Only #6 progressive supranuclear palsy and #7 mouse model still maintained a high degree of activity until now. In timeline view of Top-AAS, there was a total of 11 clusters. #0 American football, #1 brain injury, #2 tau, #3 league players, #6 phosphorylation and #9 epidemiology had been active since 2005, and #4 brain injury, #5 central nervous system, #7 mouse model, #8 repetitive brain trauma and #10 21st century brain bank had received attention since 2012. Notably, #0 American football, #3 league players, #6 phosphorylation, #7 mouse model and #11 catastrophic injury were relatively frontier research direction, which has received widespread attention today.

Overlaps between Top-cited and Top-AAS articles

There were 44 articles that overlapped between Top-cited and Top-AAS articles, indicating the 44 articles both had high citations and high AASs. We called them High-High articles in the following discussion and more details were available in the Supplementary Table S3. From Table 4, There were 36 articles were cited 90 to 499 times, 5 were cited 500 to 999 times, and 3 were cited ≥1,000 times. Among the High-High articles, 35 articles with AASs between 79 and 499, 4 articles with AASs between 500 to 999, and 5 articles with AASs of ≥1,000. It was evident that the average citation count and the average AAS of these High-High articles were significantly high, averaging at 317.89 and 476.2, respectively. There was a moderate correlation ($r = 0.415^{**}$, $p < 0.01$) between citation numbers and AASs in the High-High articles. Most of the High-High articles were open access ($n = 40$). A considerable proportion of the High-High articles had more than 4 collaborating institutions ($n = 36$) and more than 5 authors ($n = 33$). Over half of the High-High articles ($n = 25$) published in journals with impact factor greater than 10. As for study design, the most common type of the High-High articles was observational study ($n = 20$), followed by review ($n = 12$). As for the characteristics of title, there were over half of High-High articles ($n = 27$) with number of words in title shorter than 12, nearly 1/3 articles ($n = 12$) with titles separated by a colon or ended with a question mark, and nearly 1/3 articles ($n = 12$) had declarative titles that used a verb (usually past tense or present tense).

Discussion

Over the last few decades, there has been an amount of breakthrough about CTE research, including biomarkers for differential

TABLE 2 Characteristics the top-cited and top-AAS articles.

Characteristics		Top-cited	Top-AAS
Citation	Citation ≥1,000	$n = 3$	$n = 3$
	Citation 500–999	$n = 5$	$n = 5$
	Citation 90–499	$n = 92$	$n = 36$
	Citation 1–89	–	$n = 56$
	Average citation	244.88	157.54
AAS	AAS ≥1,000	$n = 5$	$n = 5$
	AAS 500–999	$n = 4$	$n = 12$
	AAS 80–499	$n = 34$	$n = 83$
	AAS 0–79	$n = 57$	–
	Average AAS	225.49	341.6
Correlation of AASs and citation numbers		$r = 0.36^{**}$, $p < 0.01$	$r = 0.247^{*}$, $p < 0.05$
AAS source	Twitter	71.65	118.88
	News	29.43	43.84
	Blog	3.24	3.61
	Facebook	4.18	5.06
	Wiki	1.37	1.06
	Google	0.86	1.03
Observational study	Basic study	$n = 25$	$n = 25$
	Case control	$n = 11$	$n = 17$
	Case report	$n = 5$	$n = 8$
	Case series	$n = 7$	$n = 6$
	Cohort study	$n = 5$	$n = 13$
	Cross-sectional	$n = 0$	$n = 3$
	Review	$n = 47$	$n = 28$
Open access		$n = 82$	$n = 89$

diagnosis (12), *in-vivo* positron emission tomography (PET) tau imaging (11), neuropathological diagnosis criteria (8), and tau filaments structures determination (13). These developments were evidenced by the vast number of articles published on CTE. Although there were some bibliometric or altmetric studies on CTE in the literature (25–27), this study is the first of its kind to combine bibliometric and altmetric analysis that may provide a more comprehensive understanding of the CTE field. In this study, we identified the characteristics of total CTE articles and examined the traits and commonalities/differences between Top-cited and Top-AAS articles. We also found there were 44 articles that overlapped between Top-cited and Top-AAS articles and reported the characteristics of them. This study revealed the shared and distinct research interests in CTE among academia and the general public, and could provide researchers with suggestions and inspirations that might enhance the impact of their research work about CTE in the future.

Topic of interest in the scientific community and the general public

Through Top-cited and Top-AAS articles, we could see that there was considerable overlap between the topics covered by the two representative lists. From the common keywords list that appeared in Top-cited and Top-AAS articles (Table 3), we could observe that both the general public and the scientific community were particularly interested in the risk factors for neurodegenerative diseases such as CTE, AD, and dementia, especially the role of injury and concussion in their development. It is important to note that not all head injuries lead to CTE, and the exact relationship between head trauma and CTE is still not fully understood (31). The link between injuries, concussions, and CTE has become a major area of research in recent years, particularly in the context of professional sports. Furthermore, numerous studies indicated a correlation between traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD), and demonstrated role of TBI in rendering individuals more susceptible to developing PTSD (32, 33). Moreover, we also found that the pathology of CTE captured the attention of the general public and scientific community. The accumulation of abnormal tau protein in the brain into neurofibrillary tangles is one of hallmarks of CTE (34). In addition to CTE, abnormal aggregation of tau protein also occurs in other neurodegenerative diseases like AD and dementia (32, 35). They may differ in the location, morphology, and severity of aggregation (12). More research is still needed to explore the specific mechanisms and impacts of tau aggregation in these neurodegenerative diseases. Besides, we could see from Figure 4 that mouse model is the research frontiers in the

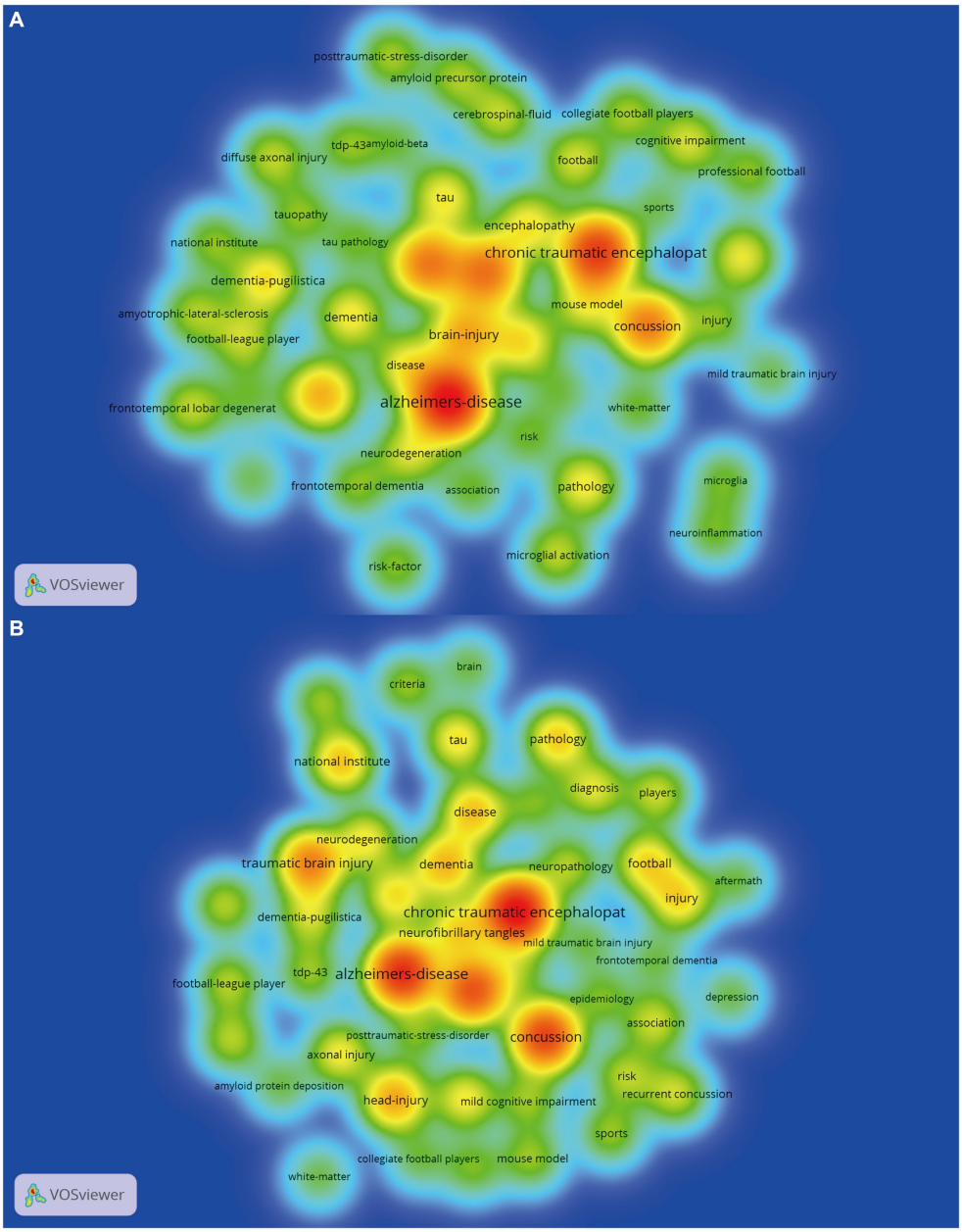

FIGURE 3
Keywords density visualization map of Top-cited **(A)** vs. Top-AAS **(B)** articles by VOSviewer software. "chronic traumatic encephalopathy," "Alzheimer's disease," "traumatic brain injury," "concussion" and "brain-injury" were the hot topics both appeared in the Top-cited map and Top-AAS map.

field of CTE and garnered both public and scientific attention. Establishing CTE-like disease in models (non-impact head acceleration, blast wave, weight drop, fluid percussion, and controlled cortical impact models) could provide a better understanding of neurobiological molecular pathways (36).

Substantial differences were also found between the characteristics of Top-cited and Top-AAS articles. By analyzing the unique keywords list in Top-cited articles, we could know that scientists were interested in studying the causes and characteristics of neurodegenerative diseases. Diffuse axonal injury, microglial activation, accumulation of amyloid precursor protein, neuroinflammation, and formation of beta-amyloid plaques are key factors in the development and progression of CTE. These factors may interact with each other, leading to dysfunction and death of brain cells (37). Research into these pathological features of CTE is ongoing, and investigating the underlying mechanisms may provide important insights into potential therapeutic targets for the disease.

However, from the unique keywords list in Top-AAS articles, we could know the general public has become increasingly concerned about the detection and prevention of CTE. Diagnosing CTE requires examining brain tissue under a microscope to detect the presence of specific neuropathological features, and there is currently no reliable method for diagnosing CTE in a living person (8). However, identifying ante-mortem prognosis of CTE instead of post-mortem

TABLE 3 Information of keywords with keywords density visualization map.

	keywords
The common keywords list in Top-cited and Top-AAS articles (According to VOSviewer keyword density visualization map)	chronic traumatic encephalopathy Alzheimer-disease (AD) concussion traumatic brain injury post-traumatic stress disorder brain-injury head-injury dementia disease pathology football neurofibrillary tangles tau encephalopathy neurodegeneration
The unique keywords list in Top-cited articles	diffuse axonal injury microglial activation amyloid precursor protein microglia neuroinflammation risk-factor amyloid-beta
The unique keywords list in Top-AAS articles	diagnosis criteria neuropathologic assessment epidemiology

diagnosis is of significant societal importance. PET imaging is being studied as a potential tool for detecting early signs of the disease in living individuals by detecting the concentration of tracer injected into the body (11). Recently, Boston University CTE Center examined the association between antemortem tracer flortaucipir-PET uptake and postmortem p-tau neuropathology in six deceased former elite American football players. Findings from this PET-to-autopsy case series suggested that PET tracer flortaucipir may be useful for detecting high stage CTE neuropathology (38). In future, more research is needed to refine this technique and develop it into a reliable diagnostic tool for CTE.

The shared characteristics of High-High articles

There were 44 articles that overlapped between the Top-cited and Top-AAS articles. The 44 High-High articles displayed both high number of citations and high AASs, indicating that these articles had both significant scholarly impact and great public attention. It can be concluded that certain topics or findings in CTE field have captured the attention of both the scientific community and the general public. This phenomenon did not appear in other similar studies (23, 24, 39). By examining the shared characteristics of High-High articles, we identified certain traits that may potentially contribute to their high citation rates and high AASs.

Journal impact: After conducting our analysis, we found that a significant portion of the High-High articles were featured in journals with notably high impact factors, such as *Nature, Science, JAMA, Lancet, New England Journal of Medicine,* and *British Journal of Sports Medicine*. This observation implied that publishing in a journal with a higher impact factor may be a viable strategy for achieving High-High outcomes, as is the case in other fields (40, 41).

Scientific collaboration: In 44 High-High articles, most article possessed more than five authors and involved three or more research institutions. Our analysis revealed a compelling link between research collaboration (individual or institutional) and the attainment of High-High outcomes. A number of studies found that multi-authorship increases above all the probability to be cited by others (42), and papers published by the cooperation of authors from several organizations gather significantly more citations than papers authored by authors from one organization (43, 44). Besides, it is maintained that papers with international collaboration have a greater impact than papers with national collaborations because of their greater quality and prestige (45). However, in High-High articles, institutional cooperation was still limited to Boston University and Harvard University, and remained primarily domestic cooperation within the United States. The strong international collaborations with other nations or regions have not found and they have not formed such a dense collaboration network. As noted in a previous bibliometric analysis of CTE, it was imperative that institutions from around the globe were motivated to engage in the discourse surrounding sports-related CTE and provide their diverse viewpoints (26). This will enable the establishment of a more comprehensive and diverse international network of collaborations, beyond the United States, to further advance the understanding and knowledge of CTE.

Study design: Our analysis revealed that observational studies were the most prevalent in High-High articles. Most of the observational studies were on diagnoses features (neuropathological and clinical) of CTE. However, typically, review papers tend to garner more impacts than research papers (43). AAS reflects the impact of disseminating research based on the interests of the general public, exhibiting greater interest in common clinical medicine topics than in complex, fundamental issues. The study subjects involved in these observational studies were the core population in the field of CTE that attracted public attention and spark discussion. These observational studies acted as building blocks of research and predominated among classics. The article titled "Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football" published in *JAMA* July 25, 2017 with extremely high score 4,770 reported that 110 of 111 (99%) former football players were suspected of having CTE (19). Another article titled "The spectrum of disease in chronic traumatic encephalopathy" analyzed post-mortem brains obtained from a cohort of 85 subjects with histories of repetitive mild traumatic brain injury and found evidence of CTE in 68 subjects (46). These observational studies with stunning results and conclusions have sent shockwaves through the scientific environment and the general public.

Characteristics of the title: Through analyzing the title of High-High articles, we found that many article titles have certain characteristics, including brevity (Number of words in titles <12), attention-grabbing (Presence of a colon or question in title), and accuracy (Declarative: used a verb). An attractive, simple, understandable, concise, and informative title for articles might be more attractive to readers (47). This phenomenon in other

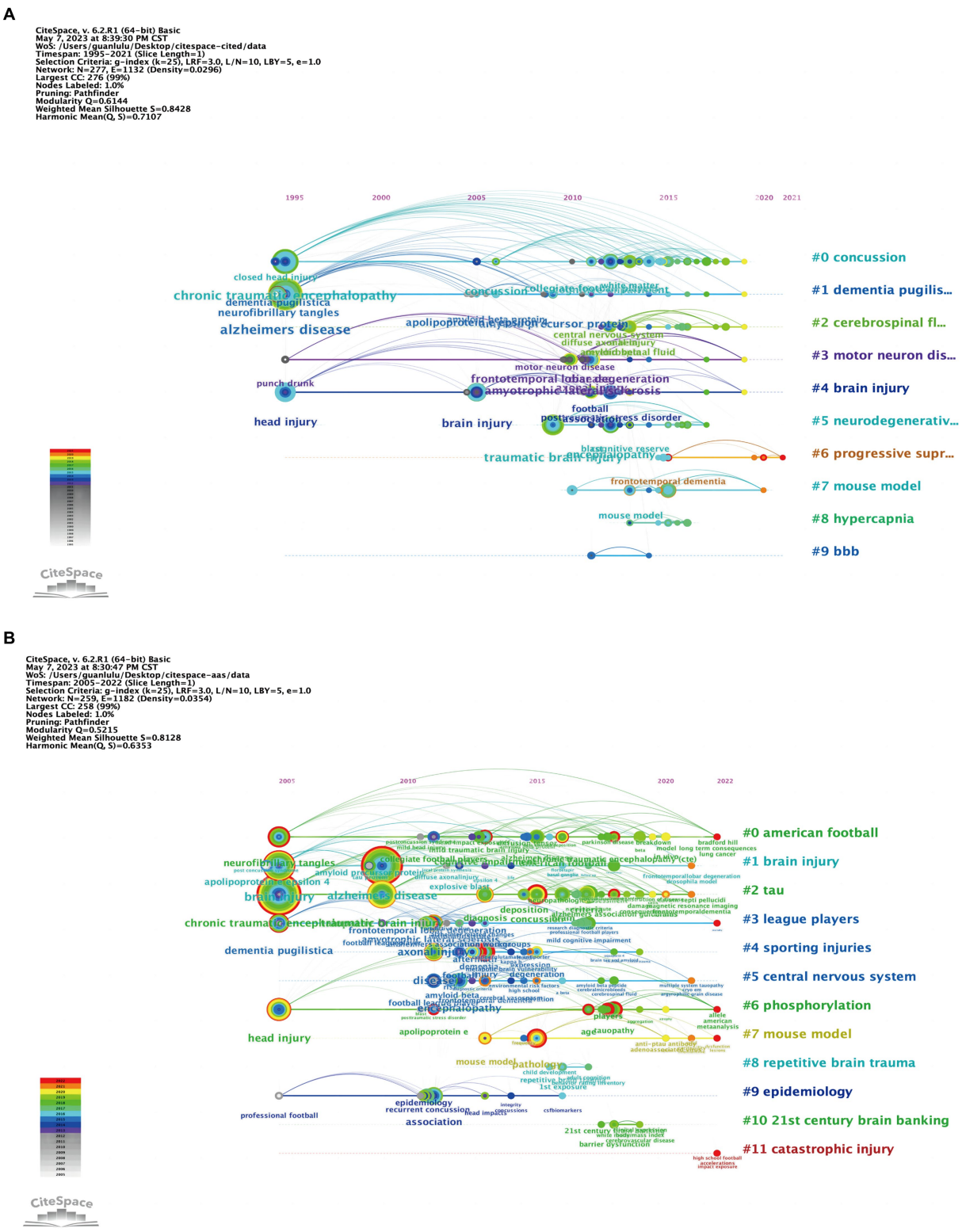

FIGURE 4
Timeline view of Top-cited **(A)** vs. Top-AAS **(B)** articles. This view represents the appearance of clusters at different time points and time spans. In timeline view of Top-cited **(A)**, there was a total of 9 clusters. In timeline view of Top-AAS **(B)**, there was a total of 11 clusters.

disciplines also applied to our research, which the titles of High-High articles were more readable than titles that use complex terminologies. There was evidence that articles with shorter titles were more likely to have advantages of citations (40, 48, 49). and articles with declarative/interrogative titles were associated with higher AASs (40, 50). However, due to the limited scope of our research, more specialized

TABLE 4 Characteristics the high-high articles.

Characteristics		Results
Citation	Citation ≥1,000	$n = 3$
	Citation 500–999	$n = 5$
	Citation 90–499	$n = 36$
	Average citation	317.89
AAS	AAS ≥1,000	$n = 5$
	AAS 500–1,000	$n = 4$
	AAS 79–499	$n = 35$
	Average AAS	476.2
Correlation of AASs and citation numbers		$r = 0.415^{**}$, $p < 0.01$
AAS source	Twitter	78.56
	News	29.89
	Blog	2.89
	Facebook	2.78
	Wiki	1.56
	Google	2.56
Open access		$n = 40$
Affiliations ≥4		$n = 36$
Authors ≥5		$n = 33$
Journal IF >10		$n = 25$
Study design	Observational study	$n = 20$
	Review	$n = 15$
Number of words in titles ≤12		$n = 27$
Presence of a colon or question in title		$n = 12$
Declarative title (used a verb)		$n = 12$

studies of association between characteristics of tile and article impact, especially with higher sample size, are required to generalize the findings of our study.

Accessibility of papers: In our study, most of High-High articles were open access. Papers published in open access journals were cited more often in comparison to papers published in non-open access journals (51, 52). The impact of open access is not only reflected in citation, the potential for more extensive research dissemination inherent in the open access option may translate into greater reach and social media attention (53). When an article is more accessible, it has the potential to reach more readers and be cited more frequently, ultimately increasing its visibility and impact within its field.

Sharing activities on social media: We have tracked the AAS sources of the High-High articles, and found that news was a great contributor to the overall score. Our study provided objective evidence that these topics received a great deal of attention in prominent news media outlets such as CNN news, Yahoo, and TIMES. Besides, Twitter activity was one of the major contributors to the final AAS of almost all articles, which was consistent with other studies (54–56). We discovered that in addition to comments from the general public, many tweets about an article also came from official Twitter accounts of its published journal (@ScienceMagazine, @NaturePortfolio, @NEJM @JAMA_current and @Brain1878), research institution (@ShorterLabGrou, @UCSFmac, @Carter_Lab, @MADLab1, and @bu_cte), author team, and other relevant journals. In the era of social media today, various scholar organizations and individuals can use platforms such as Twitter/Blog to share their views and opinions, and promote their research results and perspectives. Moreover, many journals themselves have their own official Twitter accounts, particularly top journals such as *Lancet, JAMA, Nature,* and *Science*, and tweet their recent articles regularly. Many studies from other disciplines have confirmed the effectiveness of Twitter in increasing the impact of articles (57–60). The role of social platforms in the dissemination of research is being increasingly recognized.

In summary, through analyzing the High-High articles of Top-cited and Top-AAS, we summarized the commonalities, including: publishing in high-impact journals; having multilateral collaborations; observational studies; having attractive titles; open access; and using social media tools (Figure 5). It might provide valuable insights for researchers to improve the quality and impact of their future studies in CTE field.

Associations between number of citations and AASs

Unlike findings reported by other similar studies(61–63), our results showed significant positive correlations between AAS and citation with varied strength for all 788 articles, Top-cited, Top-AAS, and High-High datasets. This difference between our work and other study may attribute to the differential research field. Although such associations were observed in our study, there was uncertainty surrounding the ability of the AAS score to accurately reflect traditional bibliometrics. Moreover, it is crucial to emphasize that online attention can be positive or negative. A controversial article may garner public interest, thereby increase the AAS of the article, while the impact of the article on the scientific community might not align with the level of public attention. Thus, AAS should be used as a complementary measure to aid researchers in appraising social media presence and evaluate the quality and impact of an article along with traditional metrics.

In the last, as previous study mentioned, several journals including *the American Journal of Epidemiology*, have appointed associate editors of social media to enhance conversations about the work they publish on social media (64). We would recommend that journals and researchers use various methods of social media promotion. Meanwhile, there is a need for increased incorporation of experimental study designs to better determine the effectiveness of different communication strategies across various channels. Twitter, News, Facebook, infographics, blog posts, virtual abstracts, and podcasts, each of these modalities has its unique characteristics and audience, and may have different effects on dissemination and readership of research findings. Today, the impact of a scientific work extends far beyond traditional citation metrics. An article might be read in order to create its value in clinical decision-making, academic educational content, educational content for the general public, development of a policy document or a guideline, public discourse and awareness, etc. Confronted with the crucial issue of CTE in people's daily lives, CTE researchers should pay more attention to social media to introduce scientific achievements in simple and easy-to-understand language, and convey the value and significance of science to the public. Furthermore, researchers and policymakers could connect the public

FIGURE 5
The shared characteristics of High-High articles.

and academics to improve public understanding of CTE related knowledge, and share clinical guides to enhance public health.

Conclusion

This study presented bibliometric and altmetric overviews of CTE-linked literature and compared the most discussed articles on CTE, highlighting the similarities and differences in the understanding of CTE between the scientific community and the general public. There was a moderate correlation between AASs and citation numbers of the total articles we gathered. Both the general public and the scientific community were particularly interested in the risk factors and pathology of CTE, and scientists were interested in studying the causes and characteristics of neurodegenerative diseases while the public has become increasingly concerned about the detection and prevention of CTE. We determined that there was considerable overlap between articles that scientists and the general public most concerned, and analyzed the potential shared characteristics of the overlapped articles. This study, which combines altmetric and traditional metrics, may provide a more comprehensive description of scientific research output, offering a point of reference for future CTE research in the selection of study topics and directions.

Limitations

A possible limitation of this type of study was that a single database may lead to some missed publications and limit the scope of the analyses and results. It might be possible to find different insights if a larger sample of articles was included. In further studies, more various databases, such as Google Scholars, will be considered to collect data. Another limitation was the time dependence of both citation and social media mentions. The number of citations tends to increase with time, and citations rarely decrease. Unlike citations, the AAS is dynamic and can rise or fall. Lastly, given altmetric data's recency bias, emerging research is more likely to be tweeted because Twitter was not available as a platform before 2007.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

LG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. JT: Data curation, Formal analysis, Methodology, Writing – review & editing. BQ: Data curation, Formal analysis, Software, Visualization, Writing – review & editing. YC: Formal analysis, Software, Visualization, Writing – review & editing. ET: Data curation, Formal analysis, Writing – review & editing. JP: Conceptualization, Investigation, Supervision, Writing – review &

editing. YZ: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1294125/full#supplementary-material

References

1. McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. (2009) 68:709–35. doi: 10.1097/NEN.0b013e3181a9d503

2. Martland HS. Punch drunk. *JAMA*. (1928) 91:1103–7. doi: 10.1001/jama.1928.02700150029009

3. Chen ST, Siddarth P, Merrill DA, Martinez J, Emerson ND, Liu J, et al. FDDNP-PET tau brain protein binding patterns in military personnel with suspected chronic traumatic encephalopathy. *J Alzheimers Dis*. (2018) 65:79–88. doi: 10.3233/JAD-171152

4. McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. *Alzheimers Dement*. (2014) 10:S242. doi: 10.1016/j.jalz.2014.04.003

5. Weiner MW, Friedl KE, Pacifico A, Chapman JC, Jaffee MS, Little DM, et al. Military risk factors for Alzheimer's disease. *Alzheimers Dement*. (2013) 9:445–51. doi: 10.1016/j.jalz.2013.03.005

6. Kelly JP, Priemer DS, Perl DP, Filley CM. Sports concussion and chronic traumatic encephalopathy: finding a path forward. *Ann Neurol*. (2023) 93:222–5. doi: 10.1002/ana.26566

7. Smith DH, Johnson VE, Trojanowski JQ, Stewart W. Chronic traumatic encephalopathy—confusion and controversies. *Nat Rev Neurol*. (2019) 15:179–83. doi: 10.1038/s41582-018-0114-8

8. McKee AC, Stein TD, Huber BR, Crary JF, Bieniek K, Dickson D, et al. Chronic traumatic encephalopathy (CTE): criteria for neuropathological diagnosis and relationship to repetitive head impacts. *Acta Neuropathol*. (2023) 145:371–94. doi: 10.1007/s00401-023-02540-wTurk

9. Montenigro PH, Baugh CM, Daneshvar DH, Mez J, Budson AE, Au R, et al. Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimers Res Ther*. (2014) 6:68. doi: 10.1186/s13195-014-0068-z

10. Lenihan MW, Jordan BD. The clinical presentation of chronic traumatic encephalopathy. *Curr Neurol Neurosci Rep*. (2015) 15:23. doi: 10.1007/s11910-015-0541-5

11. Ayubcha C, Revheim ME, Newberg A, Moghbel M, Rojulpote C, Werner TJ, et al. A critical review of radiotracers in the positron emission tomography imaging of traumatic brain injury: FDG, tau, and amyloid imaging in mild traumatic brain injury and chronic traumatic encephalopathy. *Eur J Nucl Med Mol Imaging*. (2021) 48:623–41. doi: 10.1007/s00259-020-04926-4

12. Bergauer A, Van Osch R, Van Elferen S, Gyllvik S, Venkatesh H, Schreiber R. The diagnostic potential of fluid and imaging biomarkers in chronic traumatic encephalopathy (CTE). *Biomed Pharmacother*. (2022) 146:112602. doi: 10.1016/j.biopha.2021.112602

13. Shi Y, Zhang W, Yang Y, Murzin AG, Falcon B, Kotecha A, et al. Structure-based classification of tauopathies. *Nature*. (2021) 598:359–63. doi: 10.1038/s41586-021-03911-7

14. Morin A, Davis R, Darcey T, Michael M, Benoit M, Fiona C. Subacute and chronic proteomic and phosphoproteomic analyses of a mouse model of traumatic brain injury at two timepoints and comparison with chronic traumatic encephalopathy in human samples. *Mol Brain*. (2022) 15:62. doi: 10.1186/s13041-022-00945-4

15. Trueger NS, Thoma B, Hsu CH, Sullivan D, Peters L, Lin M. The altmetric score: a new measure for article-level dissemination and impact. *Ann Emerg Med*. (2015) 66:549–53. doi: 10.1016/j.annemergmed.2015.04.022

16. Chang J, Desai N, Gosain A. Correlation between altmetric score and citations in pediatric surgery core journals. *J Surg Res*. (2019) 243:52. doi: 10.1016/j.jss.2019.05.010

17. Elmore SA. The Altmetric attention score: what does it mean and why should I care? *Toxicol Pathol*. (2018) 46:252–5. doi: 10.1177/0192623318758294

18. Thelwall M, Haustein S, Larivière V, Sugimoto CR. Do altmetrics work? Twitter and ten other social web services. *PloS One*. (2013) 8:e64841. doi: 10.1371/journal.pone.0064841

19. Mez J, Daneshvar DH, Kiernan PT, Abdolmohammadi B, Alvarez VE, Huber BR, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*. (2017) 318:360–70. doi: 10.1001/jama.2017.8334

20. Baek S, Yoon DY, Lim KJ, Hong JH, Moon JY, Seo YL, et al. Top-cited articles versus top altmetric articles in nuclear medicine: a comparative bibliometric analysis. *Acta Radiol*. (2020) 61:1343–9. doi: 10.1177/0284185120902391

21. O'Connor EM, Nason GJ, O'Kelly F, Manecksha RP, Loeb S. Newsworthiness vs scientific impact: are the most highly cited urology papers the most widely disseminated in the media? *BJU Int*. (2017) 120:441–54. doi: 10.1111/bju.13881

22. Suzan V, Bektan Kanat B, Yavuzer H, Doventas A. Themes and trends for osteoporosis: the bibliometric and altmetric approach. *Arch Osteoporos*. (2021) 16:122. doi: 10.1007/s11657-021-00983-w

23. Park S, Blackledge K, Ananth C, Sauer M, Brandt J. Altmetric and bibliometric analysis of influential articles in reproductive biology, 1980–2019. *Reprod Biomed Online*. (2022) 45:384–90. doi: 10.1016/j.rbmo.2022.04.005

24. Grover S, Elwood AD, Patel JM, Ananth CV, Brandt JS. Altmetric and bibliometric analysis of obstetrics and gynecology research: influence of public engagement on citation potential. *Am J Obstet Gynecol*. (2022) 227:300.e1–300.e44. doi: 10.1016/j.ajog.2022.03.013

25. Qi B, Jin S, Qian H, Zou Y. Bibliometric analysis of chronic traumatic encephalopathy research from 1999 to 2019. *Int J Environ Res Public Health*. (2020) 17:5411. doi: 10.3390/ijerph17155411

26. Wolfson DI, Kuhn AW, Kerr ZY, Brett BL, Yengo-Kahn AM, Solomon GS, et al. Chronic traumatic encephalopathy research viewed in the public domain: what makes headlines? *Brain Inj*. (2020) 34:528–34. doi: 10.1080/02699052.2020.1725843

27. Eagle SR, Okonkwo DO. Telling the whole story: bibliometric network analysis to evaluate impact of media attention on chronic traumatic encephalopathy research. *J Neurotrauma*. (2023) 40:148–54. doi: 10.1089/neu.2022.0266

28. STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Available at: https://www.equator-network.org/reporting-guidelines/strobe/

29. Van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Forensic Sci*. (2010) 84:523–38. doi: 10.1007/s11192-009-0146-3

30. Chen C. *Mapping scientific Frontiers*. London, LDN: Springer (2013).

31. Paul M, Willem HM, Mark A, Bob C, Jiří D, Ruben JE, et al. Consensus statement on concussion in sport: the 4th international conference on concussion in sport held in Zurich, November 2012. *Br J Sports Med*. (2013) 47:250–8. doi: 10.1136/bjsports-2013-092313

32. Gillam W, Godbole N, Sangam S, DeTommaso A, Foreman M, Lucke-Wold B. Neurologic injury-related predisposing factors of post-traumatic stress disorder: a critical examination. *Biomedicine*. (2023) 11:2732. doi: 10.3390/biomedicines11102732

33. Lucke-Wold B, Nolan R, Nwafor D, Nguyen L, Cheyuo C, Turner R, et al. Post-traumatic stress disorder delineating the progression and underlying mechanisms following blast traumatic brain injury. *J Neurosci Neuropharmacol*. (2018) 4:118.

34. McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Dirk Keene C, Litvan I, et al. The first NINDS/NIBIB consens us meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*. (2016) 131:75–86. doi: 10.1007/s00401-015-1515-z

35. Sriram S, Lucke-Wold B. Advances research in traumatic encephalopathy. *Biomedicine*. (2022) 10:2287. doi: 10.3390/biomedicines10092287

36. Turner RC, Lucke-Wold BP, Logsdon AF, Robson MJ, Lee JM, Bailes JE, et al. Modeling chronic traumatic encephalopathy: the way forward for future discovery. *Front Neurol*. (2015) 6:223. doi: 10.3389/fneur.2015.00223

37. Cherry JD, Tripodis Y, Alvarez VE, Huber B, Kiernan PT, Daneshvar DH, et al. Microglial neuroinflammation contributes to tau accumulation in chronic traumatic encephalopathy. *Acta Neuropathol Commun*. (2016) 4:112. doi: 10.1186/s40478-016-0382-8

38. Alosco ML, Su Y, Stein TD, Protas H, Cherry JD, Adler CH, et al. Associations between near end-of-life flortaucipir PET and postmortem CTE-related tau neuropathology in six former American football players. *Eur J Nucl Med Mol Imaging*. (2023) 50:435–52. doi: 10.1007/s00259-022-05963-x

39. Banshal SK, Basu A, Singh VK, Muhuri PK. Scientific vs. public attention: a comparison of top cited papers in WoS and top papers by Altmetric score In: M Erdt, editor. *Communications in Computer and Information Science*, vol. *856*. Singapore, SG: Springer Singapore (2018)

40. Didegah F, Bowman TD, Holmberg K. On the differences between citations and altmetrics: an investigation of factors driving altmetrics versus citations for finnish articles. *J Assoc Inf Sci Technol*. (2018) 69:832–43. doi: 10.1002/asi.23934

41. Araujo AC, Vanin AA, Nascimento DP, Gonzalez GZ, Costa LOP. What are the variables associated with Altmetric scores? *Syst Rev*. (2021) 10:193. doi: 10.1186/s13643-021-01735-0

42. Glänzel W, Debackere K, Thijs B, Schubert A. A concise review on the role of author self-citations in information science, bibliometrics and science policy. *Forensic Sci*. (2006) 67:263–77. doi: 10.1007/s11192-006-0098-9

43. Tahamtan I, Safipour Afshar A, Ahamdzadeh K. Factors affecting number of citations: a comprehensive review of the literature. *Forensic Sci*. (2016) 107:1195–225. doi: 10.1007/s11192-016-1889-2

44. Puuska H-M, Muhonen R, Leino Y. International and domestic co-publishing and their citation impact in different disciplines. *Forensic Sci*. (2014) 98:823. doi: 10.1007/s11192-013-1181-7

45. Sooryamoorthy R. Do types of collaboration change citation? A scientometric analysis of social science publications in South Africa. *Forensic Sci*. (2017) 111:379–400. doi: 10.1007/s11192-017-2265-6

46. McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. (2013) 136:e255. doi: 10.1093/brain/awt051

47. Rostami F, Mohammadpoorasl A, Hajizadeh M. The effect of characteristics of title on citation rates of articles. *Forensic Sci*. (2014) 98:2007–10. doi: 10.1007/s11192-013-1118-1

48. Letchford A, Moat HS, Preis T. The advantage of short paper titles. 2015. *R Soc Open Sci*. (2015) 2:150266. doi: 10.1098/rsos.150266

49. Deng B. Papers with shorter titles get more citations. *Nature*. (2015) 2:150266. doi: 10.1038/nature.2015.18246

50. Araujo AC, Nascimento DP, Gonzalez GZ, Maher CG, Costa LOP. Impact of low back pain clinical trials measured by the altmetric score: cross-sectional study. *J Med Internet Res*. (2018) 20:e86. doi: 10.2196/jmir.9368

51. Alkhawtani RHM, Kwee TC, Kwee RM. Citation advantage for open access articles in European radiology. *Eur Radiol*. (2020) 30:482–6. doi: 10.1007/s00330-019-06389-0

52. Hua F, Sun H, Walsh T, Glenny AM, Worthington H. Open access to journal articles in oncology: current situation and citation impact. *Ann Oncol*. (2017) 28:2612–7. doi: 10.1093/annonc/mdx398

53. Vadhera AS, Lee JS, Veloso IL, Khan ZA, Trasolini NA, Gursoy S, et al. Open access articles garner increased social media attention and citation rates compared with subscription access research articles: an altmetrics-based analysis. *Am J Sports Med*. (2022) 50:3690–7. doi: 10.1177/03635465221124885

54. Kolahi J, Khazaei S, Iranmanesh P, Khademi A, Nekoofar MH, Dummer PMH. Altmetric analysis of the contemporary scientific literature in Endodontology. *Int Endod J*. (2020) 53:308–16. doi: 10.1111/iej.13226

55. Studenic P, Ospelt C. Do you tweet?: trailing the connection between Altmetric and research impact! *RMD Open*. (2020) 6:e001034. doi: 10.1136/rmdopen-2019-001034

56. Wang J, Alotaibi NM, Ibrahim GM, Kulkarni AV, Lozano AM. The spectrum of altmetrics in neurosurgery: the top 100 "trending" articles in neurosurgical journals. *World Neurosurg*. (2017) 103:883. doi: 10.1016/j.wneu.2017.04.157

57. Nabavi M. An analysis of journalism articles achieving high Altmetric attention scores. *Learned Publishing*. (2022) 35:617–24. doi: 10.1002/leap.1492

58. Moon JY, Yun EJ, Yoon DY, Seo YL, Cho YK, Lim KJ, et al. Analysis of the altmetric top 100 articles with the highest altmetric attention scores in medical imaging journals. *Jpn J Radiol*. (2020) 38:630–5. doi: 10.1007/s11604-020-00946-0

59. Garcovich D, Ausina Marquez V, Adobes MM. The online attention to research in periodontology: an Altmetric study on the most discussed articles on the web. *J Clin Periodontol*. (2020) 47:330–42. doi: 10.1111/jcpe.13221

60. Jeong JW, Kim MJ, Oh H-K, Jeong S, Kim MH, Cho JR, et al. The impact of social media on citation rates in coloproctology. *Colorectal Dis*. (2019) 21:1175–82. doi: 10.1111/codi.14719

61. Delli K, Livas C, Nikitakis NG, Vissink A. Impact of COVID-19 dentistry-related literature: an altmetric study. *Int Dent J*. (2023) 73:770–6. doi: 10.1016/j.identj.2022.11.005

62. Collins CS, Singh NP, Ananthasekar S, Boyd CJ, Brabston E, King TW. The correlation between altmetric score and traditional bibliometrics in orthopaedic literature. *J Surg Res*. (2021) 268:705–11. doi: 10.1016/j.jss.2021.07.025

63. Fox ES, McDonnell JM, Kelly A, Cunniffe GM, Darwish S, Bransford R, et al. The correlation between altmetric score and traditional measures of article impact for studies pertaining to spine trauma. *Eur Spine J*. (2023) 1–7. doi: 10.1007/s00586-023-07962-4

64. Fox MP, Carr K, D'Agostino McGowan L, Murray EJ, Hidalgo B, Banack HR. Will podcasting and social media replace journals and traditional science communication? No, but. *Am J Epidemiol*. (2021) 190:1625–31. doi: 10.1093/aje/kwab172

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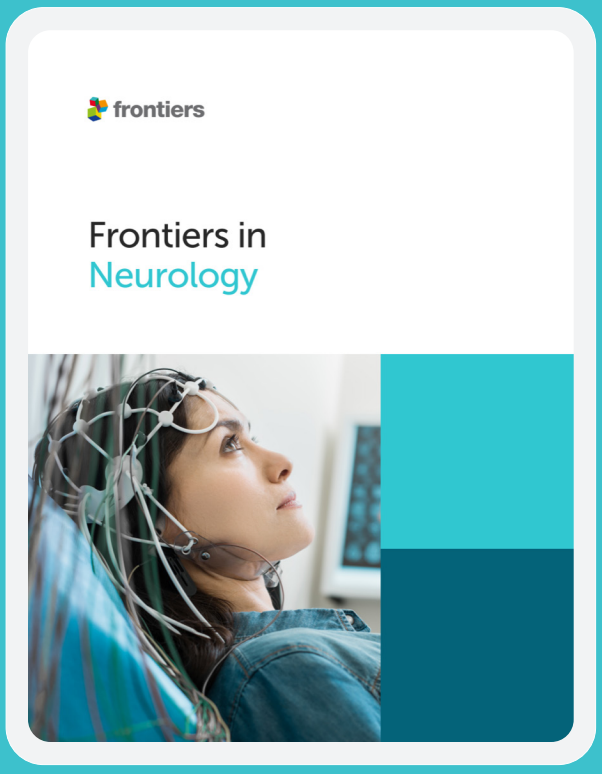

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