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Assessment and treatment interventions for traumatic brain injury

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Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-6980-1
DOI 10.3389/978-2-8325-6980-1

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Assessment and treatment interventions for traumatic brain injury

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Citation
Lavender, A. P., Takechi, R., Hellewell, S. C., Kawata, K., eds. (2025). *Assessment and treatment interventions for traumatic brain injury*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-6980-1

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frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 29 September 2025
DOI 10.3389/fneur.2025.1696541

OPEN ACCESS

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RECEIVED 01 September 2025
ACCEPTED 15 September 2025
PUBLISHED 29 September 2025

CITATION
Lavender AP, Takechi R, Hellewell SC and Kawata K (2025) Editorial: Assessment and treatment interventions for traumatic brain injury. *Front. Neurol.* 16:1696541. doi: 10.3389/fneur.2025.1696541

Editorial: Assessment and treatment interventions for traumatic brain injury

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KEYWORDS

brain injury, traumatic brain injury (TBI), brain injury assessment, mild traumatic brain injury (mTBI), chronic traumatic encephalopathy (CTE)

Editorial on the Research Topic
Assessment and treatment interventions for traumatic brain injury

Introduction

Traumatic brain injury (TBI) results from a blow to the head or other sudden head movement, often caused by collisions, falls, or impacts during sport, military service, or motor vehicle accidents.

Treatment options depend on severity, but mild TBI is frequently under-reported and often left untreated, particularly in sports where quick return-to-play is prioritized. Current assessment tools are limited in guiding safe recovery decisions, highlighting the need for improved evaluation methods. Rehabilitation strategies also require ongoing assessment and refinement to optimize recovery across the spectrum of injury severity.

This Research Topic invited contributions focused on assessment and intervention strategies for mild, moderate, and severe TBI. Twenty-one articles addressing TBI assessment and treatment in the form of original research, reviews, and a case report have been included.

Preclinical insight: animal studies and mechanistic findings

Animal studies contribute greatly to critical mechanistic insights that inform development of interventions for rehabilitation following TBI. A study explored the long-term effects of decompressive craniectomy in TBI using a mouse model (Szczygielski et al.). Mice were divided into four groups: sham, craniectomy alone, TBI alone, and TBI with craniectomy. Neurological function and brain oedema were assessed over 28 days.

Results showed that craniectomy following TBI worsened early neurological outcomes and increased brain oedema, transitioning from cytotoxic to vasogenic with gliosis. Craniectomy alone also caused delayed oedema and gliosis. Although the negative effects were transient, findings suggest that craniectomy may aggravate brain injury, and future treatments should aim to reduce post-surgical brain swelling to improve recovery.

TBI may disrupt thalamo-cortical pathways, triggering inflammation and vascular damage that contribute to neurodegeneration. Özen et al. explored the role of interleukin-1β (IL-1β) in capillary alterations and pericyte coverage in the thalamus and cortex following TBI. Using a central fluid percussion injury model in adult male C57BL/6 mice, researchers administered either a neutralizing anti-IL-1β antibody or a control antibody post-injury. Immunohistochemical analysis at 2 and 7 days revealed that early inhibition of IL-1β signaling prevented capillary damage and enhanced pericyte coverage in the thalamus, suggesting IL-1β plays a key role in post-TBI vascular pathology.

Clinical prognostic tools and outcomes research

Network analysis was used in a study to examine symptom relationships in patients with mild traumatic brain injury (mTBI) treated at U.S. Level 1 trauma centers (Eagle et al.). Researchers analyzed Rivermead Post-Concussion Symptoms Questionnaire data from 1,593 patients at 2 weeks and 3, 6, and 12 months post-injury. Cognitive symptoms had the highest influence early on, while fatigue became most influential at 12 months. Emotional symptoms also showed significant influence, although network structure remained stable over time. Early symptom patterns were more predictive of long-term recovery and quality of life than traditional clinical factors, suggesting cognitive, emotional, and fatigue symptoms may be key targets for mTBI treatment.

A retrospective study by Generoso et al. examined risk factors for breakthrough early post-traumatic seizures (PTS) in patients with TBI receiving phenytoin prophylaxis. Among 105 patients in an intensive care unit (ICU), early PTS occurred more frequently in older individuals, those with higher Marshall Computed Tomography scores, and those undergoing neurosurgery for hematoma evacuation. Despite therapeutic phenytoin levels in most cases, seizures still occurred, and nearly half lacked level monitoring. Early PTS was associated with longer ICU stays and increased hospital mortality. These findings suggest that certain clinical factors may predict seizure risk despite prophylaxis, highlighting the need for improved monitoring and alternative strategies to prevent early PTS in TBI patients.

The study by Tang et al. included in this Research Topic developed and validated a nomogram to predict 28-day mortality in patients with skull fractures using data from the Medical Information Mart for Intensive Care (MIMIC) database with data from the eICU Collaborative Research Database used for external validation. A total of 1,527 adult patients were analyzed. Predictive factors included age, temperature, serum sodium, mechanical ventilation, vasoactive agents, mannitol use, extradural hematoma, loss of consciousness, and Glasgow Coma Scale (GCS) score. The model demonstrated strong performance, with AUCs of 0.857 and 0.853 and C-index values of 0.832 and 0.829 in training and validation sets, respectively. Calibration and decision curve analyses confirmed clinical utility, offering a reliable tool for early mortality risk assessment in skull fracture patients.

High sodium levels in TBI patients in ICUs are linked to poor prognosis, but research on optimal sodium levels and their impact on early mortality using the MIMID-IV database is limited. A retrospective study included in this Research Topic analyzed 1,749 TBI patients from the MIMIC-IV database to assess the impact of serum sodium levels on in-hospital mortality (Wang X. et al.). Patients with hypernatremia (sodium >145 mmol/L) had significantly higher mortality (25.3%) than those with lower levels (9.3%). A non-linear, L-shaped relationship was found, with mortality risk increasing sharply beyond 144.1 mmol/L. Even after adjusting for clinical variables, hypernatremia remained an independent predictor of death. These findings highlight the importance of monitoring and managing sodium levels in TBI patients, suggesting that targeted sodium control may improve outcomes and reduce early mortality.

TBI remains a major global health concern, particularly in low- and middle-income countries, where fatality rates are high despite existing guidelines. A key factor in severe TBI outcomes is elevated intracranial pressure (ICP), which can cause brain herniation and death. Timely diagnosis and management of ICP are critical in neuro-intensive care. Monitoring ICP offers real-time insights that help reduce secondary brain damage and improve survival. However, accurate interpretation still relies heavily on clinical expertise. This review article by Zhang et al. explores global disparities in TBI, the role and challenges of ICP monitoring, decompressive craniectomy, and the importance of personalized treatment approaches.

Treatment/intervention trials

Systematic reviews provide particularly helpful insights into recent research. Kawata et al. evaluated randomized controlled trials on pharmacological, stimulation, and exercise-based interventions for chronic symptoms following TBI. Despite extensive research, pharmacological treatments—particularly neurostimulants like Modafinil and Armodafinil—showed inconsistent results in managing fatigue and sleep disturbances. In contrast, brain stimulation techniques (e.g., transcranial magnetic stimulation and blue light therapy) and exercise interventions demonstrated more consistent benefits for cognitive and mental health symptoms. However, most studies had small sample sizes, limiting their clinical impact. The review highlights the need for larger, high-quality trials to better understand and optimize treatment strategies for chronic TBI-related symptoms.

The next study in this Research Topic is a randomized, double-blind clinical trial that evaluated biperiden as a potential intervention to prevent post-traumatic epilepsy (PTE) in adults with acute TBI (Foresti et al.). Between 2018 and 2022, 123 participants were randomized to receive biperiden or placebo for 10 days, with outcomes assessed over 24 months. It is important to note that the trial was halted early due to the COVID-19 pandemic. Analysis showed no significant effect of biperiden on PTE incidence or mortality. Notably, the biperiden group experienced a higher

frequency of late seizures. These findings suggest insufficient evidence for biperiden's efficacy in preventing PTE, highlighting the need for larger, more comprehensive studies on the use of biperiden as an intervention for PTE in adults with acute TBI.

A systematic review and meta-analysis evaluated the effects of amantadine on TBI recovery using data from six randomized controlled trials involving 426 patients (Félix et al.). Results showed that amantadine significantly improved GCS scores in patients than controls who received a placebo on day 7. Mini Mental State Examination Scores also improved indicating enhanced cognitive recovery. However, no significant differences were found in Disability Rating Scale, early GCS scores, Glasgow Outcome Scale, hospital stay length, or ventilation duration. While amantadine shows promise for short-term cognitive improvement in TBI patients, its broader impact on functional recovery remains uncertain and warrants further investigation.

The retrospective cohort study by Gao et al. investigated the impact of thiamine administration on in-hospital mortality among 1,755 TBI patients admitted to the ICU. Using data from the MIMIC-IV database, researchers found that thiamine use was significantly associated with reduced mortality, even after adjusting for confounding factors. Subgroup analysis revealed particularly strong benefits for patients aged 65 and older, males, and those with severe TBI. The findings suggest that thiamine may offer a protective effect in critical care settings for TBI patients, supporting its potential role in improving survival outcomes. Further research is needed to confirm these results.

Functional and psychosocial outcomes

The study of Nicolau de Costa et al. assessed color discrimination in 10 cognitively normal TBI patients using a fixed saturation test and CT scans to locate brain lesions. All patients performed well with high saturation stimuli. However, four with ventral stream lesions and one with occipital damage showed impaired discrimination at low saturation. Those with dorsal stream lesions performed similarly to controls. The findings suggest that low saturation color discrimination deficits are linked to ventral brain damage and may serve as a functional tool for evaluating visual impairment in TBI patients.

Exertional tests have been suggested as a useful tool for assisting clinicians in the management of concussion. Some of these are expensive or require highly skilled clinical expertise for operation. The Multimodal Exertional Test (MET) was developed by Pyndiura et al. to assess concussion-related exertion using minimal resources. It includes four progressive stages combining physical and cognitive tasks. In a pilot study with 14 healthy interuniversity athletes, heart rate (HR) and symptom severity were monitored. HR increased from baseline to Stage 1 and again from Stage 3 to 4, with no significant changes between Stages 1 to 3. Female athletes showed higher HRs than males throughout. All participants reported minimal symptom changes. The MET effectively induced exertion without symptom provocation, suggesting its potential utility in concussion management with limited clinical resources.

mTBI can significantly impact patients' lives. Understanding the knowledge and attitudes of patients and their families is a crucial step toward enhancing patient care and management. The work of He et al. presents a cross-sectional study at Zhejiang Hospital in China that surveyed 573 individuals using an online questionnaire to assess mTBI knowledge and attitudes. Average knowledge and attitude scores were 11.00 (range: 0–20) and 27.78 (range: 8–40), respectively. Lower scores were associated with a middle school education and moderate-income levels, while personal experience with mTBI from falls correlated with more positive attitudes. These findings highlight gaps in awareness and the need for targeted, accessible education to improve understanding and attitudes toward mTBI, ultimately enhancing patient care and recovery outcomes.

TBI is a major cause of death and disability, especially in low- and middle-income countries (LMICs), where healthcare resources are limited. The original research study included in the Research Topic tested low-cost, scientifically validated tools—including paper-based and modified computer tasks—to identify post-TBI deficits in 51 patients and 20 controls across four Ethiopian hospitals (Semework et al.). Tests assessed cognitive and visual impairments, with the Montreal Cognitive Assessment (MoCA) proving especially effective. Results showed these methods can detect deficits in processing speed, memory, and executive function. The findings support the feasibility of implementing such tools in LMICs and highlight the need for dedicated rehabilitation centers.

The study by Wang J. et al. compared nurse-led and neurologist-led care for patients recovering from craniotomy due to TBI. Reviewing records of 230 patients over 6 months, researchers found that nurse-led care significantly improved activities of daily living, quality of life, and reduced anxiety, depression, and caregiver burden compared with neurologist-led care. Patients under nurse-led care also reported fewer complications, such as pressure sores and dizziness. These findings suggest that nurse-led follow-up care is not only effective but may surpass neurologist-led care for certain outcomes, highlighting its potential for improving long-term recovery and support in resource-limited settings.

Neuropsychological evaluation is the strongest predictor of functional outcomes in TBI patients. While research on TBI diagnosis and treatment has grown rapidly, there is a lack of comprehensive, practical neuropsychological reviews. Chan et al. provide another review that expands beyond standard overviews by examining the rationale behind neuroimaging choices and recent findings on neuropsychological assessments and their link to recovery. It includes tables detailing recovery trajectories across age groups, associated risk factors, and promising cognitive rehabilitation tools. Phenomenological studies are also discussed. The review concludes by identifying research gaps and suggesting future directions to enhance clinical understanding and treatment of TBI.

Case reports and rare conditions

Chronic subdural hematoma (CSDH) is typically linked to trauma but rarely associated with nephrotic syndrome. This case report describes a patient with nephrotic syndrome who developed CSDH (Xue, Xue et al.). Laboratory tests revealed hypoproteinemia and hyperlipidemia, confirming nephrotic syndrome. The patient underwent successful trepanation and drainage of the

hematoma, followed by atorvastatin treatment. After neurological improvement, the patient was transferred for nephrotic syndrome management. No neurological issues were observed at a 3-month follow-up. The case suggests nephrotic syndrome may contribute to CSDH and highlights the importance of timely surgical intervention and coordinated care for optimal recovery.

The next article describes a retrospective study comparing clinical characteristics of traumatic and not otherwise specified (NOS) chronic CSDH in 301 patients (Yang et al.). Traumatic CSDH patients were generally younger, more likely to experience seizures, and less likely to be on anticoagulant or antiplatelet medications. They also had a higher rate of asymptomatic presentation. Despite these differences, both groups showed similar radiological findings at admission, received comparable treatments, and had equivalent clinical outcomes. The study highlights distinct patient profiles for traumatic vs. NOS CSDH but suggests that treatment approaches and prognoses remain consistent across both types.

Penetrating brain injuries are rare but highly lethal and disabling forms of neurosurgical trauma. Skull base injuries caused by arrows are especially uncommon and typically accidental, though self-inflicted cases are rising. This report presents a unique case of a suicidal transoral arrow injury penetrating the brain (Xue, Li et al.). It emphasizes the importance of preoperative imaging for surgical planning and confirms surgery as an effective treatment. The study also reviews previous case reports to offer clinical recommendations for detecting and managing such injuries, highlighting the need for careful assessment and tailored intervention strategies in these complex and life-threatening cases.

An opinion article by Omer et al. discussed a study on management and treatment of patients with traumatic tension pneumocephalus and the challenges of treating people with brain injury in low- and middle-income countries (1). The authors clearly describe the condition, explaining that it is a compressive effect caused by air trapped on the brain, and recent studies that have explored possible techniques for resolving the condition. The authors suggest that the priority should be to reduce hospital stays and risk of post-operative complications and that this is most likely achieved using endonasal endoscopic approaches for first-line treatment. They argue that this method is preferred since it is the least invasive approach, prioritizes efficiency and safety, and is accessible to people in low- and middle-income countries.

Together, this collection of articles adds significant knowledge and advances our understanding of various aspects of assessment and treatment of TBI using human and animal original studies as well as reviews, case reports, and an interesting opinion article.

Author contributions

AL: Writing – original draft, Writing – review & editing. RT: Writing – review & editing. SH: Writing – review & editing. KK: Writing – review & editing.

Conflict of interest

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The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Publisher's note

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 20 November 2023
DOI 10.3389/fneur.2023.1308683

OPEN ACCESS

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RECEIVED 06 October 2023
ACCEPTED 01 November 2023
PUBLISHED 20 November 2023

CITATION
Szczygielski J, Hubertus V, Kruchten E, Müller A, Albrecht LF, Schwerdtfeger K and Oertel J (2023) Prolonged course of brain edema and neurological recovery in a translational model of decompressive craniectomy after closed head injury in mice. *Front. Neurol.* 14:1308683.
doi: 10.3389/fneur.2023.1308683

Prolonged course of brain edema and neurological recovery in a translational model of decompressive craniectomy after closed head injury in mice

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Background: The use of decompressive craniectomy in traumatic brain injury (TBI) remains a matter of debate. According to the DECRA trial, craniectomy may have a negative impact on functional outcome, while the RescueICP trial revealed a positive effect of surgical decompression, which is evolving over time. This ambivalence of craniectomy has not been studied extensively in controlled laboratory experiments.

Objective: The goal of the current study was to investigate the prolonged effects of decompressive craniectomy (both positive and negative) in an animal model.

Methods: Male mice were assigned to the following groups: sham, decompressive craniectomy, TBI and TBI followed by craniectomy. The analysis of functional outcome was performed at time points 3d, 7d, 14d and 28d post trauma according to the Neurological Severity Score and Beam Balance Score. At the same time points, magnetic resonance imaging was performed, and brain edema was analyzed.

Results: Animals subjected to both trauma and craniectomy presented the exacerbation of the neurological impairment that was apparent mostly in the early course (up to 7d) after injury. Decompressive craniectomy also caused a significant increase in brain edema volume (initially cytotoxic with a secondary shift to vasogenic edema and gliosis). Notably, delayed edema plus gliosis appeared also after decompression even without preceding trauma.

Conclusion: In prolonged outcomes, craniectomy applied after closed head injury in mice aggravates posttraumatic brain edema, leading to additional functional impairment. This effect is, however, transient. Treatment options that reduce brain swelling after decompression may accelerate neurological recovery and should be explored in future experiments.

KEYWORDS

mouse model, brain edema, decompressive craniectomy, traumatic brain injury, magnetic resonance imaging, closed head injury

Introduction

The aim of decompressive craniectomy (DC) is to reduce intracranial pressure (ICP) by removing part of the skull (1). DC may be performed for a variety of indications (1, 2), and traumatic brain injury (TBI) remains the flagship condition for which neurosurgeons are employing DC (3, 4), usually due to posttraumatic brain edema (5–8).

The positive effects of skull decompression in TBI are not exclusively mechanistic. In addition to reducing ICP (5, 9–11) and optimizing intracranial compliance (12, 13), DC is capable of improving cerebral blood flow, cerebrovascular reactivity, brain tissue oxygenation and cerebral metabolism (3, 5, 14, 15). However, the clinical data on functional recovery after TBI and DC remain controversial. The results of randomized clinical trials (DECRA and RESCUEicp) are not equvocal: DECRA demonstrated that DC increases the risk of an unfavorable posttraumatic course (16), while RESCUEicp reported improved recovery due to craniectomy (17). Importantly, RESCUEicp as well as some smaller studies demonstrated that the positive effect of DC increases over time (3, 17, 18).

This inconsistency in results of major clinical trials on DC may be only partially explained by differences (regarding the protocols and the population of patients) between both studies (DECRA vs. RESCUEicp). Therefore, a detailed analysis of the course of pathophysiological changes after TBI / DC in controlled setting of the translational animal model remains a valid research option. However, translating the dynamic effects of posttraumatic craniectomy into animal experiments remains a challenging task (19–24). In previous experiments, we were able to establish a mouse model of DC based on the closed head injury (CHI) paradigm (25, 26). In short-term observations, decompression performed early after CHI increased contusional blossoming, promoted brain edema formation and aggravated functional impairment (27). Until now, temporal dynamics in our murine DC model were followed only in a short time period (up to 3d) (28). We hypothesize that the effects of craniectomy on trauma sequelae will change their intensity over the prolonged course in animal experiments, as they do in clinical settings. To address this issue, we performed a series of experiments, observing neurological impairment and brain edema evolution at remote time points.

Methods

Animals and trauma model

The study was planned and performed according to ARRIVE guidelines (29) and in line with the laws for animal protection, including Directive 2010/63/EU, after approval of the local ethical board (17/2013, Saarland Ethical Commission).

Abbreviations: ADC, apparent diffusion coefficient; BBS, beam balance score; BBT, beam balancing time; CCI, controlled cortical impact; CSF, cerebrospinal fluid; CHI, closed head injury; DC, decompressive craniectomy; DWI, diffusion weighted image; FPI, fluid percussion injury; GFAP, glial fibrillary acidic protein; ICP, intracranial pressure; ICU, intensive care unit; MRI, magnetic resonance imaging; NSS, neurological severity score; RCT, randomized controlled trial; ROI, region of interest; TBI, traumatic brain injury.

Application of trauma according to the closed head injury (CHI) paradigm and microsurgical decompression of the left cerebral hemisphere was performed in male wild-type, CD-1 mice (9–12 weeks old, Charles River Laboratories) as described previously (for a detailed animal handling protocol and detailed description of the surgical procedure, see Supplementary material S1). Animals were randomly assigned to one of the following experimental groups: 1. sham-operated (sham); 2. decompressive craniectomy alone (DC); 3. closed head injury alone (CHI); 4. CHI followed by DC at 1 h post-TBI (CHI+DC) ($n = 8$ surviving animals in each group).

Surgical procedures were performed under isoflurane anesthesia and under monitoring of vital parameters, including body and head temperature. For groups CHI and CHI+DC, experimental TBI of moderate-to-severe degree was induced using a weight drop device [adapted from Chen et al. (25)]. Briefly, after inducing anesthesia and surgical exposure of the intact skull by skin incision, a 75 g weight was dropped from a height of 30 cm on a silicone cone resting on the exposed skull, resulting in focal brain injury to the left hemisphere. In the CHI+DC group, unilateral DC was performed 1 h after trauma as described previously (27): Here, after a midline longitudinal skin incision, the area of the skull over traumatized hemisphere was exposed. Thereafter, the temporal muscle was detached from its origin over the temporal bone, allowing additional exposition of temporal squama down to the floor of the middle fossa. Here, a margin of bone flap to be removed was outlined in the parietal and temporal bone using a dental drill (under constant cooling by the irrigation of the normal saline). Both parts of parietal and temporal bone were then removed down to the skull base and a dura opening over the hemisphere was created using microscissors and microforceps. Thereafter, the dura was left open, the muscle was freely readapted and the skin was closed using 5–0 polypropylene sutures. After hemostasis was achieved by temporary application of the gelatin foam, the skin was suture closed. In the DC group, the same procedure was performed (including incision and peeling off the dura parts) on the nontraumatized brain/skull 1 h following sham injury.

Neurological assessment

The functional status of the animals was evaluated by an observer blinded to the treatment applied. The neurological severity score (NSS) (as the more complex neurobehavioral score) and beam balance score (BBS) (focused mostly on vestibular and motor function) were used (26, 30). For NSS, a 10-point scale was adapted from Stahel et al. (31). Animals were awarded one point for failure to perform a task. In the BBS, animals were awarded from 0 (good performance) to 5 points (not attempting to balance) during three attempts [adapted from Mikawa et al. (32)], and the mean was used for further analysis. The total balancing time (60 s each attempt = max 180 s) was analyzed separately.

NSS and beam balance performance, including BBS and beam balancing time (BBT), were assessed at the following time points: 1 day (24 h), 3 days (72 h), 7 days, 14 days and 28 days after the start of surgery.

Magnetic resonance imaging

After functional assessment at each of the time points (1d, 3d, 7d, 14d and 28d), animals were subjected to magnetic resonance imaging

(MRI), described and published in detail as an open-access protocol elsewhere (see Supplementary material 2 for detailed description) (33). In brief, MRI scanning was performed under isoflurane anesthesia with constant monitoring of vital parameters. MR sequences were acquired according to multislice multiecho (MSME, T1 weighted), turbo spin echo (TSE, T2 weighted) and echo planar imaging (DWI, diffusion weighted) paradigms.

Brain edema was identified in T2-weighted images and acquired diffusion coefficient (ADC) maps calculated from the DWI data, and matching regions of interest (ROI) were manually created with the Paravision 5.1 ROI tool. The resulting size measurements (in pixels and mm^2) were exported, and the total volume of the lesions was calculated.

Histological analysis

Twenty-eight days after surgical treatment, the animals were sacrificed using transcardial perfusion with buffered formaldehyde solution; the brains were removed, fixed, and paraffin embedded, and serial coronal sections of the brains (5 µm) were made, presenting ROIs, i.e., coronal slices displaying hippocampal areas CA1 and CA3, as assessed using the stereotactic mouse brain atlas (34). The neighboring sections were stained with H&E (hematoxylin and eosin) as well as by the Nissl staining technique and immunostained with anti-glial fibrillary acidic protein (anti-GFAP) antibody (as described in Supplementary material S3).

All sections were microscopically analyzed by an independent observer blinded to the treatment of the animal.

Statistical analysis

For all time points (1d, 3d, 7d, 14d and 28d), the weight of the experimental animals (including Δ weight), neurological impairment according to the NSS and BBS, balancing time in the BB test (BBT) and volume of lesions were expressed as the mean ± SEM.

The Gaussian distribution was validated using the Shapiro–Wilk test. For the values with a non-Gaussian distribution and for the nonparametric values (NSS and BBS), the Kruskal–Wallis test followed by Dunn's multiple comparison *post hoc* test was applied. For the parametric values with Gaussian distribution, one-way ANOVA with Bonferroni *post hoc* correction was used. For each animal, a global injury score (as demonstrated by Δ weight, NSS, BBS, BBT, volume of edema) was created by averaging the five respective measures at single time points (1d, 3d, 7d, 14d, 28d) and analyzed across the treatment groups using the Kruskal–Wallis test or one-way ANOVA.

For analysis of both treatment and time effects, two-way ANOVA (for parametric variables with Gaussian distribution) and Friedman's two-way analysis of the variance by ranks (for nonparametric and/or non-Gaussian variables) were used, treating each mouse as a block and time as a factor (time and treatment as two independent factors). For all parts of the assessment, significance was set at $p < 0.05$.

Results

Perioperative management, mortality and morbidity

The early mortality (surgical part of the experiment, up to 3 h) was highest in the CHI+DC group (36%), followed by 33% in the CHI group, 21% in the DC group and 10% in the sham group. In the prolonged course, additional loss of experimental animals was observed, increasing total mortality numbers to 66% for the CHI+DC group, 45% in the CHI group, 53% in the DC group and 20% for sham animals.

Weight of animals

No differences in initial weight were documented between the groups. Both the weight and its changes were strongly affected by the time course (weight: one-way analysis: $p > 0.05$, ns for all groups and all time points; two-way analysis: $p > 0.05$, ns for treatment effect; $p < 0.0001$,*** for time effect; Δ weight; two-way analysis: $p = 0.22$, ns for treatment effect; $p < 0.0001$,*** for time effect; Figures 1A,B).

Functional outcome

According to NSS, animals subjected to craniectomy after trauma (CHI+DC) demonstrated the poorest global performance (Figure 2A), with the most profound impairment at the first two posttraumatic measurement points (1d and 3d after injury) and present to a lesser degree at remote time points (7d and 28d; Figure 2B). According to two-way analysis, time course significantly impacted functional recovery according to NSS (NSS; two-way analysis: $p = 0.01$,* for treatment effect; $p = 0.0027$,** for time effect).

A different pattern was seen in the analysis of BBS. Here, the average impairment score of CHI+DC animals was higher than that of sham but not DC animals (Figure 3A). In a detailed analysis of separate time points, at 1d postinjury, the trauma animals (CHI) and the DC group displayed clear deficits compared with the sham control. In CHI+DC animals, the balancing performance was poorer than that in the sham group but not the DC group. A similar pattern could be demonstrated at 3d, 14d and 28d postinjury. In contrast, in the prolonged outcome group (7d-28d), the BBS performance of the CHI group did not differ from that of the sham and DC reference groups (Figure 3B). Both treatment and time affected the beam balance performance results (BBS; two-way analysis: $p = 0.0097$,** for treatment effect; $p < 0.0001$,*** for time effect).

The analysis of averaged beam balancing time (BBT) mirrored the BBS results. Here, the average BBT of CHI+DC animals was the lowest among the groups and was significantly lower than that in the sham group but not the DC group (Figure 4A). At separate time points, BBT demonstrated the impairment of CHI+DC animals, which was significant at 1d and at 3d postinjury. At the same time points, no significant difference in balancing time could be stated between CHI animals and reference groups. At more remote time points (7d-28d), no significant differences could be discerned (Figure 4B). In two-way analysis, the effect of time but not of treatment on BBT was significant

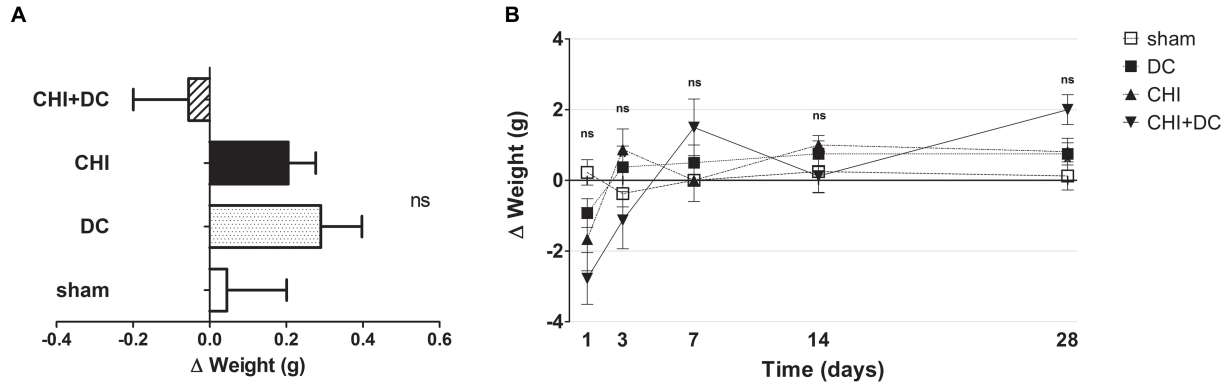

FIGURE 1
Histograms demonstrating weight loss (difference of two consecutive weightings as a more detailed parameter of well-being and recovery than plain weight assessment) after trauma/surgical treatment during the prolonged posttraumatic course (up to 28d). **(A)** The total weight loss score (obtained by averaging the weight change values assessed at separate time points) is presented. Animals treated with surgical decompression after trauma (CHI + DC) displayed a negative index, while the positive result of the calculation could be attributed to the rest of the groups, although no significant difference between the groups could be demonstrated. **(B)** Graph demonstrating the time course of weight loss/gain during the whole experiment. The most dynamic changes occurred during the first 7d of observation, with the CHI+DC group being affected by the most considerable weight loss compensated by its spectacular gain later on. However, none of the single time point comparisons revealed a significant difference between the groups.

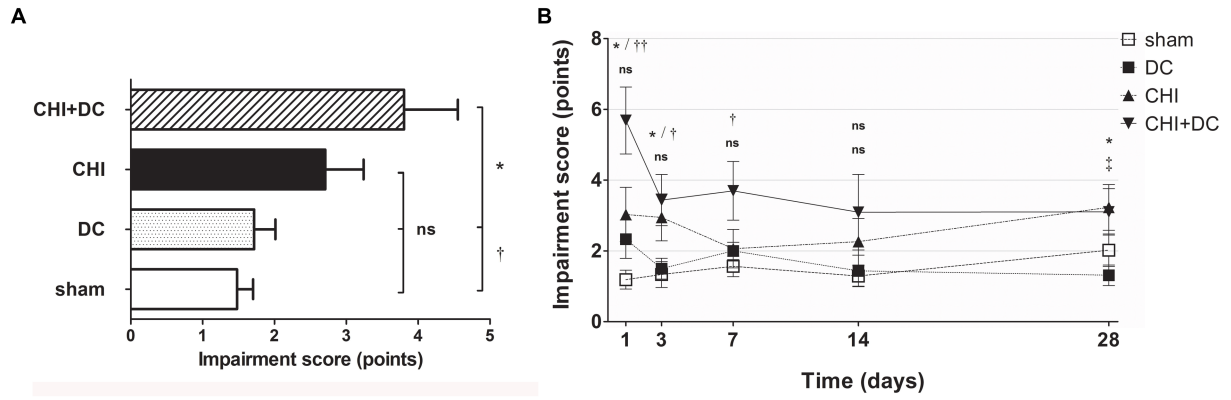

FIGURE 2
Histograms showing neurological impairment after trauma/sham injury according to the Neurological Severity Score (NSS) during the prolonged posttraumatic course (up to 28d). **(A)** The total impairment score (obtained by averaging the NSS values assessed at separate time points) is demonstrated. Animals treated with surgical decompression after trauma (CHI + DC) displayed the most profound impairment, which was significantly higher than that of the sham or decompression-only (DC) group (CHI+DC vs. DC, * $p < 0.05$; CHI+DC vs. sham, † $p < 0.05$). **(B)** Graph demonstrating the time course of neurological impairment and recovery based on NSS assessment. Note the high level of functional impairment among CHI+DC animals at 1d postinjury, concordant with our previous report (27) and successive improvement of the NSS values. The description of significant differences between the groups is double-noted; the upper index refers to the comparison between CHI+DC vs. DC (*) and CHI+DC vs. sham (†), and the lower index refers to the comparison between CHI vs. sham (§) and CHI vs. DC (‡). In the early course, there was a significant impairment of animals with posttraumatic decompression (1d CHI+DC vs. DC: *, $p < 0.05$; vs. sham: ††, $p < 0.01$; 3 d CHI+DC vs. DC: *, $p < 0.05$; CHI+DC vs. sham: †, $p < 0.05$; 7 d CHI+DC vs. sham: †, $p < 0.05$). The fluctuation of neurological recovery resulted in late impairment (28d CHI+DC vs. DC: *, $p < 0.05$). Notably, the trauma animals without craniectomy (CHI) also demonstrated delayed functional damage (28d, CHI vs. DC: ‡, $p < 0.05$).

(BBT; two-way analysis: $p = 0.07$, ns for treatment effect; $p < 0.0001$, *** for time effect).

Radiological assessment

The MRI-radiological features after different treatment combinations are presented in Figures 5–7.

As expected, sham animals demonstrated no discernible brain damage (including no brain edema formation). During the postoperative course, only proper healing of the superficial scalp wound could be demonstrated.

In contrast, the DC group demonstrated slight deformation of the cortex areas underlying the skull window as early as 1d after surgery. Initially, only the superficial cortex layer demonstrated some hyperintensity in T2-scans. However, at this time point, a restriction of fluid diffusion (suggestive of cytotoxic edema) that reached more profound areas of the cortex could be displayed in ADC images. These changes faded over time point 3d and were accompanied by appearance of smaller, ADC-hyperintense areas that resolved at time

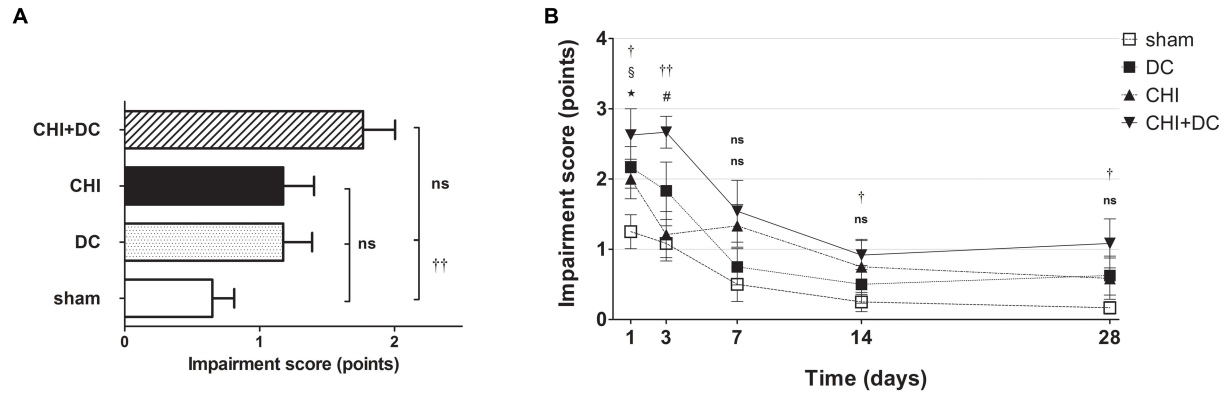

FIGURE 3
Histograms demonstrating neurological impairment after trauma/sham injury according to the Beam Balance Score (BBS) during the prolonged posttraumatic course (up to 28d). **(A)** The total impairment score (obtained by averaging the BBS values assessed at separate time points) is presented. Again, animals treated with surgical decompression after trauma (CHI + DC) had the poorest performance; however, the only significant difference was noted between this treatment group (CHI+DC) and the secondary control group (sham) (CHI+DC vs. sham: ††, $p < 0.01$). **(B)** Graph demonstrating the time course of neurological impairment and recovery based on BBS assessment. Similar to the NSS results, functional impairment was highest among CHI+DC animals in the early phase postinjury. The description of significant differences between the groups is double-noted; the upper index refers to the comparison between CHI+DC vs. DC (*) and CHI+DC vs. sham (†), the lower index refers to the comparison between CHI vs. sham (§) and CHI vs. DC (‡), and the additional symbols describe the significance of the difference between CHI+DC vs. CHI (#) and between DC vs. sham (**). The most profound impairment of CHI+DC animals was observed in the early course, as this group demonstrated poorer performance than sham littermates (1d CHI+DC vs. sham: †, $p < 0.05$; 3d CHI+DC vs. sham: ††, $p < 0.01$). In the late course, successive improvement of neurological function in all groups was seen (as demonstrated by the downward slope of the impairment curves). However, the difference between sham-treated and CHI+DC animals remained significant (saved time point 7 d): (14 d CHI+DC vs. sham: †, $p < 0.05$; 28 d CHI+DC vs. sham: †, $p < 0.05$). In the case of CHI animals, initial impairment (1d CHI vs. sham: §, $p < 0.05$) and substantial improvement between 1d and 3d were documented, leading to a significant difference between this group and trauma + craniectomy animals (3d CHI+DC vs. CHI: #, $p < 0.05$) at the latter time point. Nevertheless, statistical significance between the CHI+DC group and the primary control (DC) was lacking (CHI+DC vs. DC: ns, $p > 0.05$ for all time points). This effect was probably due to the poor performance of decompression-only animals, which was significant at 1d postinjury (1d DC vs. sham: *, $p < 0.05$).

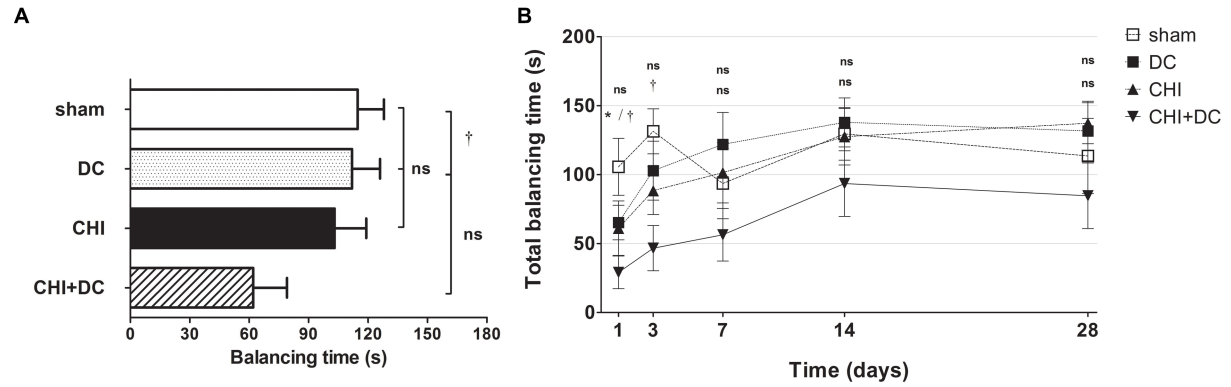

FIGURE 4
Histograms demonstrating neurological performance after trauma/sham injury according to the total balancing time in the beam balance test (BBT) during the prolonged posttraumatic course (up to 28d). Note the reversed order of groups in both parts of the figure, as the lowest scores in this **(B)** represent the most profound impairment. **(A)** The total impairment score (obtained by averaging the BBT values assessed at separate time points) is presented. Similar to the results of the NSS and BBS assessments, animals treated with surgical decompression after trauma (CHI + DC) had the poorest performance (i.e., the shortest balancing times). Similar to the BBS results, the difference between the groups was observed only between this treatment group (CHI+DC) and sham animals (CHI+DC vs. sham: †, $p < 0.05$). **(B)** Graph demonstrating the time course of neurological impairment and recovery based on BBT assessment. Again, functional impairment was highest among CHI+DC animals in the early phase postinjury. As observed previously, the most profound difference could be noted at 1d postinjury; here, both primary and secondary controls (DC and sham animals, respectively) demonstrated significantly longer balancing times than the trauma + decompression group (1d CHI+DC vs. DC: *, $p < 0.05$; vs. sham: †, $p < 0.05$). This effect could also be demonstrated at 3d after trauma in regard to the sham group (3d CHI+DC vs. sham: †, $p < 0.05$). Later, all but the sham group (with an undulating course of BBT performance score) demonstrated successive improvement with an increase in balancing times. Nevertheless, for prolonged outcomes (7d-28d), the differences between the groups were not statistically significant.

point 14d up to 28d. However, some small ADC- (and, to lesser degree, T2-) hyperintense cortical and subcortical changes remained visible up to endpoint 28d, resulting in deformation of the region underlying the craniectomy. This could be visualized in T1 images as some distortion of anatomical structures (cortical areas, corpus callosum and hippocampal area). Notably, no signs of subgaleal CSF

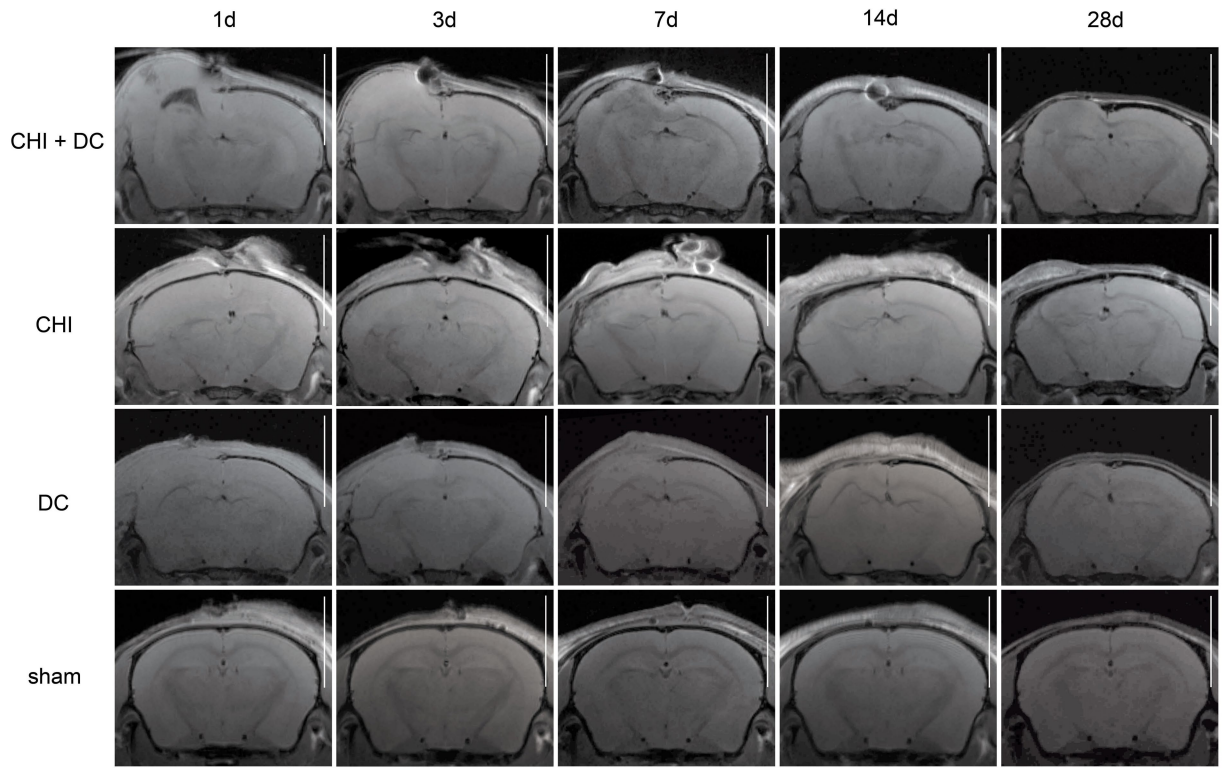

FIGURE 5
Panels of images representing the time course of radiological changes after trauma/decompressive craniectomy: time course (horizontal) vs. different treatment groups (vertical). Here, the MRI scans as T1-weighted images are presented. See description and interpretation of radiological changes in the main text. The scans were obtained in representative animals (each row demonstrates the radiological course in the same animal) using a 9.4 Tesla MRI scanner; white bar = 5 mm.

collection or changes specific for brain tissue infection could be noted in the DC group.

In the CHI group, the features of brain edema formation and parenchymal changes, typical for a murine CHI model, were displayed. Thus, an early peak of cerebral swelling (at 1d and 3d) could be demonstrated. Here, the area of increased water content was hyperintense in the T2 scan but hypointense in the ADC-weighted images, suggesting the cytotoxic character of edema. The accompanying midline shift indicated the space-occupying effect of edema. In the further course, the changes evolved to the form of ADC-mixed lesions with an increasing hyperintense component, most prominent 28d after injury.

The animals subjected to both trauma and decompression (CHI+DC) demonstrated the most striking injury pattern. Starting at the earliest time point (1d postinjury), massive swelling of the decompressed cortex, including external herniation of the cerebral tissue over the bone margin, was present. According to ADC mapping, the edema of the cortex was mostly of cytotoxic character (similar to the trauma-only group). However, at early stages, some ADC-hyperintense zones could be delineated in subcortical areas (from 1d up to 7d). Starting at 7d, the extent of external herniation subsided, and the diffuse edematous zones (initially hypointense in the ADC map) evolved into T2- and ADC-hyperintense areas, with the signal intensity increasing during the protracted course. At the same time, the subcortical hyperintense areas expanded, peaking in size and intensity at 14d with a subsequent decline toward the endpoint (28d).

In volumetric analysis, sham-treated animals did not present any discernible lesions, while CHI+DC animals demonstrated the highest volume of lesions, particularly at early time points (1d to 7d; Figures 8A,B). Notably, at early time points (1d-3d), the craniectomy-only group (DC) (CHI) also demonstrated a significant amount of ADC hypointense changes.

Regarding hyperintense changes, the CHI+DC group again demonstrated the highest magnitude of lesions. However, the craniectomy-only group also demonstrated significant lesions (Figure 9A). These changes also displayed a different progression course, with their appearance and peak starting at 7 days. As an ephemeral observation, the DC group demonstrated a significant volume of hyperintense changes at 14d (Figure 9B).

Similar results were obtained in the calculation, where both types of lesion (hypo- and hyperintense in ADC assessment) were added and analyzed as one variable. Obviously, the total lesion volume after averaging was highest in the CHI+DC group. Additionally, in the craniectomy-only group, the sum of lesion volume was higher than that in the sham group (Figure 10A). On the time axis, profound damage was observed in CHI+DC animals at all time points assessed. The DC group displayed a significant amount of total lesion at 1d, 3d and 14d after surgery (Figure 10B).

Histological analysis

Two staining methods, Nissl staining to visualize neuronal loss and GFAP immunohistochemistry to depict glial activation, were implemented. These results are demonstrated in Figures 11, 12.

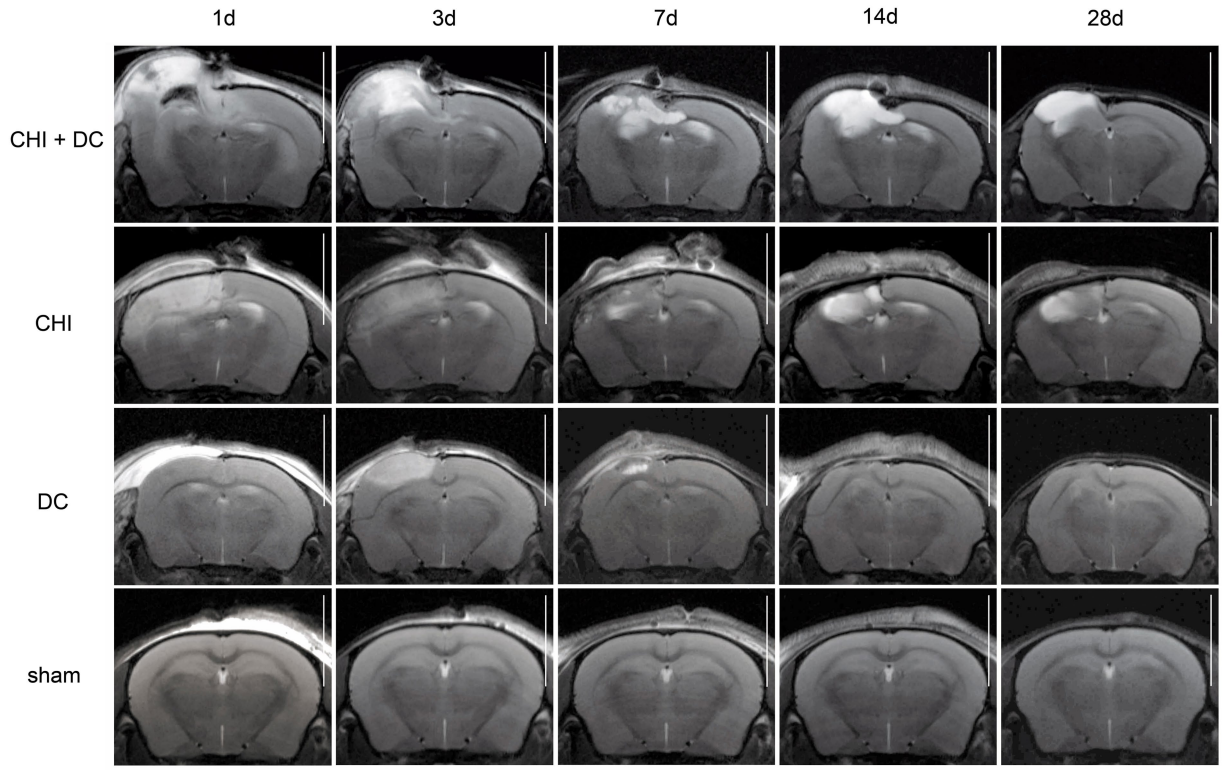

FIGURE 6
Set of images similar to Figure 5, including T2-MRI scans. See description and interpretation of radiological changes in the main text. Again, the scans were obtained in representative animals (each row demonstrates the radiological course in the same animal) using a 9.4 Tesla MRI scanner; white bar = 5 mm.

According to Nissl staining (Figure 11), no changes in neuronal density or structure could be discerned in sham-treated animals. In contrast, the craniectomy performed without trauma (DC group) led to profound thinning of cortical layers with accumulation of several pyknotic neuronal nuclei in the area adjacent to the cranial window. However, the changes in subcortical zones were rather scarce, as represented by a couple of apoptotic neurons in the pyramidal layer of the hippocampus. In contrast, in CHI animals, a dramatic increase in the number of degenerating neurons could be demonstrated both in cerebral layers and, particularly, in the hippocampal pyramidal area of CA1. Animals subjected to both trauma and craniectomy (CHI+DC) displayed the most profound changes: not only total cortical depletion at the injury epicenter but also a dramatic reduction in the population of viable neurons (in favor of degenerating nerve cells) could be observed in the adjacent cortex. Additionally, the hippocampus demonstrated substantial neuronal loss, including not only apoptotic nerve cells but also several ghost neurons, and evidence of ongoing necrotic processes could be observed.

In GFAP staining (Figure 12), sham animals demonstrated no presence of activated astroglia across cortical layers and several GFAP-positive astroglia cells in CA1 hippocampal areas, consistent with previous anatomic descriptions (35).

As to the results of GFAP staining: Decompression performed without previous trauma led to the activation of numerous cortical astroglia and a noticeable increase in the population of GFAP-positive glial cells in the hippocampus (DC; here, for better visualization of cortical glial cells, an example of an animal with a less atrophic cortex was chosen). A similar pattern was observed among animals subjected to trauma, with even more accentuated astroglia-related hippocampal changes (CHI). In trauma + craniectomy animals, the most considerable increase in the population of activated astroglia can be recognized in the cortex adjacent to its atrophied part (although the hippocampus demonstrates a substantial increase in astroglia density as well).

Discussion

In a previous series of experiments, we described the impact of craniectomy on early brain edema formation and on the short-term outcome (24 h) (27). Using the same paradigm, we expanded the follow-up timeframe to 28 days. We demonstrated a prolonged course of neurological impairment with partial recovery over time in animals with and without craniectomy. We also characterized the pattern of structural changes (gliosis and brain edema) following trauma and decompression using repetitive MRI scanning and endpoint histopathological analysis. Finally, we demonstrated the delayed negative effects of craniectomy, even without trauma.

In the past, Zweckberger et al. reported improved brain edema formation at 24 h after CCI in mice, resulting in reduced neurological impairment in the posttraumatic course (8d) (20) if the craniectomy was performed early enough (up to 3 h post-TBI) (21). In prolonged observation (28d), Friess et al. demonstrated reduced axonal damage, diminished white matter atrophy and less severe hippocampal

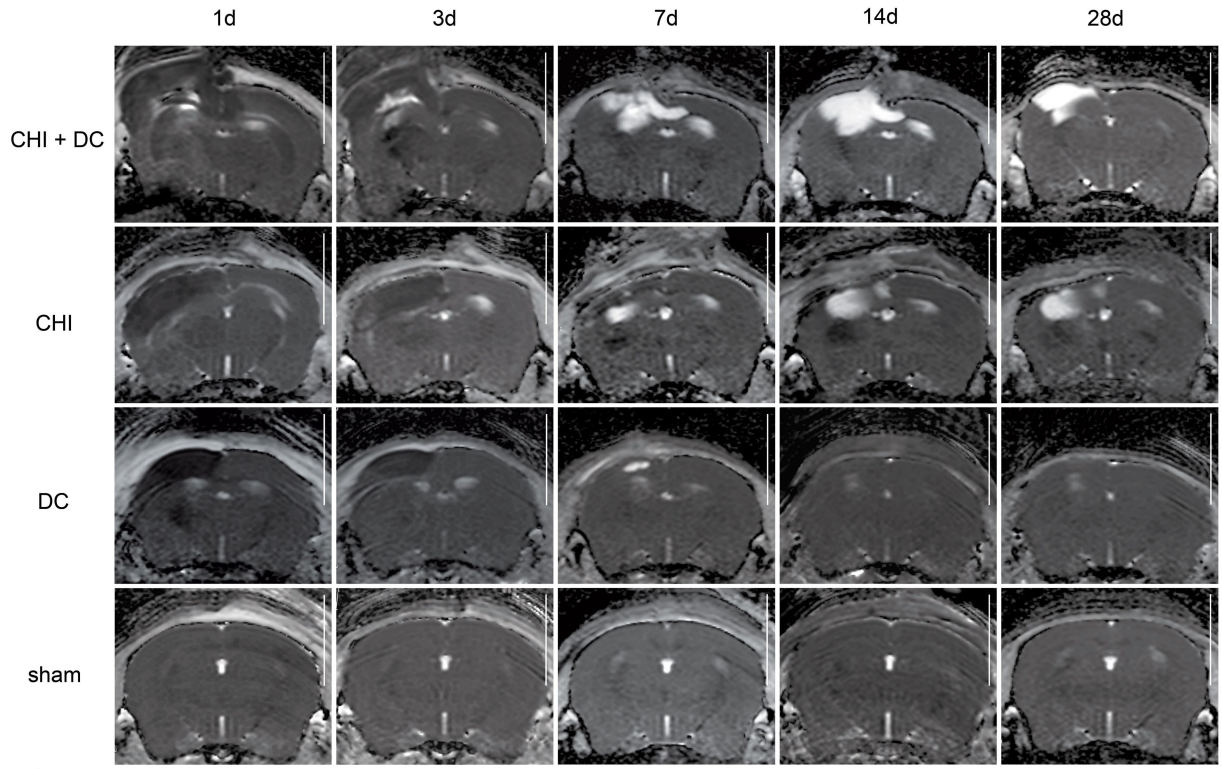

FIGURE 7
Set of images similar to Figures 5, 6, presenting ADC-MRI maps. See description and interpretation of radiological changes in the main text. Again, the scans were obtained in representative animals (each row demonstrates the radiological course in the same animal) using a 9.4 Tesla MRI scanner; white bar = 5 mm.

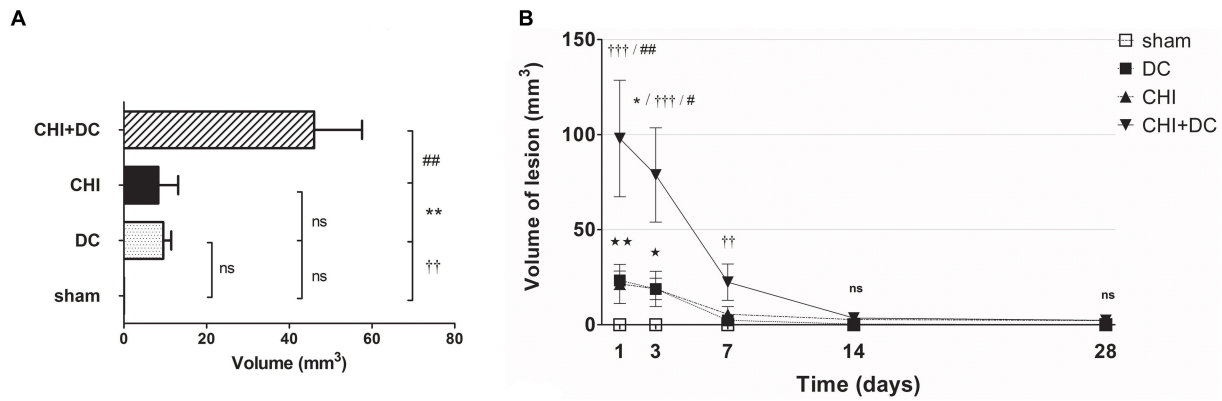

FIGURE 8
Histograms demonstrating volumetric analysis of MRI scans assessing the amount of lesion that is hypointense in ADC mapping (thus suggesting the presence of cytotoxic edema) during the prolonged posttraumatic course (up to 28d). **(A)** The averaged volume of hypointense lesions (obtained by averaging the volumetric data assessed at separate time points) is demonstrated. This type of structural change was most prominent in animals treated with surgical decompression after trauma (CHI + DC), as evidenced by a significant difference compared to all other groups (CHI+DC vs. DC, ** $p < 0.01$; CHI+DC vs. sham, †† $p < 0.01$, CHI+DC vs. CHI, ## $p < 0.01$). **(B)** Graph demonstrating the time course of ADC hypointense changes. The description of significant differences between the groups is single-noted, referring to comparisons between CHI+DC vs. DC (*), CHI+DC vs. sham (†) and CHI+DC vs. CHI (#); the additional symbols describe the significance of differences between DC vs. sham (**). Obviously, the animals treated by posttraumatic decompression displayed the highest volume of the lesion, with the early peak at the initial time point of 1d. The difference from other groups (in particular to the secondary reference, i.e., sham animals) remained significant up to 7d postinjury (1d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: ## $p < 0.01$; 3 d CHI+DC vs. DC: *, $p < 0.05$; CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: # $p < 0.05$; 7 d CHI+DC vs. sham: ††, $p < 0.01$). Notably, "true sham" animals subjected to decompression but not to trauma also displayed a significant amount of hypointense changes (1d DC vs. sham: **, $p < 0.01$; 3d DC vs. sham: *, $p < 0.05$). In all animals, this type of lesion faded with the time course, with no meaningful volume at 14d and 28d.

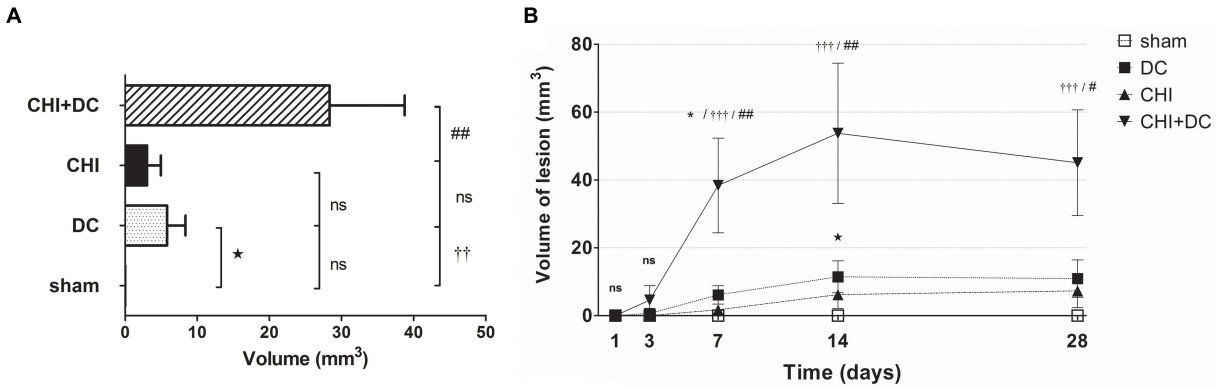

FIGURE 9
Histograms demonstrating volumetric analysis of MRI scans assessing the amount of lesion that is hyperintense in ADC mapping (thus suggesting presence of vasogenic edema, gliosis or both) during the prolonged posttraumatic course (up to 28d). **(A)** The averaged volume of hyperintense lesions (obtained by averaging the volumetric data assessed at separate time points) is presented. Similar to hypointense changes, the average lesion volume was most prominent in animals treated with surgical decompression after trauma (CHI + DC). This difference was statistically significant when compared with secondary reference (sham) as well as with trauma-only animals (CHI+DC vs. sham, ††, $p < 0.01$, CHI+DC vs. CHI, ##, $p < 0.01$) but not with primary reference (DC) animals (CHI+DC vs. DC, ns, $p > 0.05$). This observation presumably relies on a highly significant level of structural changes in the DC group itself (DC vs. sham: ★, $p < 0.05$). **(B)** Graph demonstrating the time course of ADC-hyperintense changes. The description of significant differences between the groups is single-noted, referring to comparisons between CHI+DC vs. DC (*), CHI+DC vs. sham (†) and CHI+DC vs. CHI (#); the additional symbols describe the significance of differences between DC vs. sham (★). The shape of the curves clearly demonstrates that this kind of lesion is a late phenomenon, with its peak at 14d post-trauma. Again, the highest amount of lesion was attributed to animals treated by posttraumatic decompression. The difference from other groups (in particular to the secondary reference, i.e., sham animals) became significant starting 7d postinjury (7d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: ## $p < 0.01$; 14d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: ## $p < 0.01$; 28d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: # $p < 0.05$). However, the difference from the primary reference (DC animals) became significant only at 7d after surgery (7d CHI+DC vs. DC: *, $p < 0.05$), probably due to the meaningful amount of hyperintense changes in the DC group thereafter, reaching a plateau at 14d post-surgery (14d DC vs. sham: ★, $p < 0.05$).

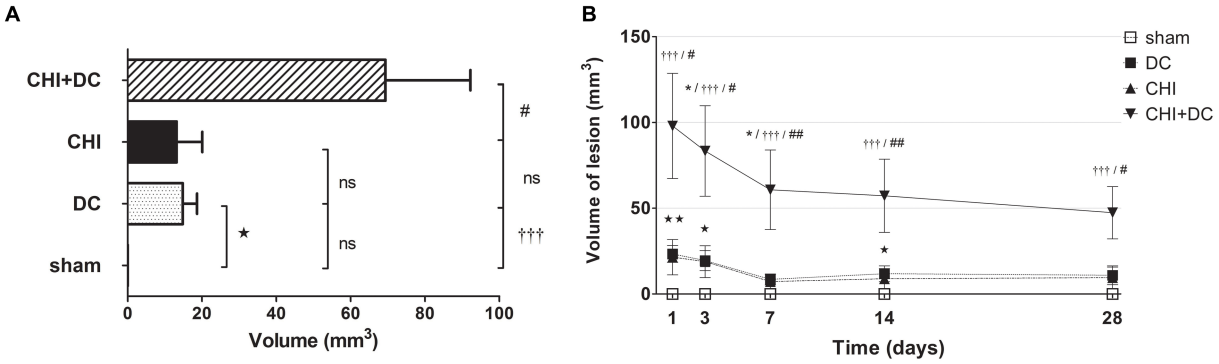

FIGURE 10
Pair of histograms demonstrating the total volume of lesions (both hypo- and hyperintense in ADC mapping) during the prolonged posttraumatic course (up to 28d). **(A)** The averaged total lesion volume (obtained by averaging the volumetric data assessed at separate time points) follows the pattern displayed by hyperintense-only changes. Thus, the total edema volume was highest in animals treated with surgical decompression after trauma (CHI + DC), and again, this difference was statistically significant when compared with secondary reference (sham) as well as with trauma-only animals (CHI+DC vs. sham, ††, $p < 0.01$, CHI+DC vs. CHI, ##, $p < 0.01$) but not with primary reference (DC) animals (CHI+DC vs. DC, ns, $p > 0.05$). After summation of both lesion types, a significant level of structural changes in the DC group was reached (DC vs. sham: ★, $p < 0.05$). **(B)** Graph demonstrating the time course of total lesion volume. The description of significant differences between the groups is single-noted, referring to comparisons between CHI+DC vs. DC (*), CHI+DC vs. sham (†) and CHI+DC vs. CHI (#); the additional symbols describe the significance of differences between DC vs. sham (★). The time course resembles that of hypointense changes, with an early peak immediately after trauma/surgery and a plateau starting at +/− 7d postinjury. In this part of the analysis, the trauma + craniectomy group demonstrated a total lesion volume that was significantly higher at all time points compared with both sham animals and the trauma-only group (1d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: # $p < 0.05$; 3d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: # $p < 0.05$; 7d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: ## $p < 0.01$, 14d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: ## $p < 0.01$; 28d CHI+DC vs. sham: †††, $p < 0.001$; vs. CHI: # $p < 0.05$). Regarding the primary reference (DCs), significance was reached only at 3d and 7d postinjury (3d CHI+DCs vs. DCs: *, $p < 0.05$; 7ad CHI+DCs vs. DCs: *, $p < 0.05$). Most importantly, this pattern results from a considerable amount of total lesion, seen in the DC group, as evidenced by significant differences at time points 1d, 3d and 14d (1 d DC vs. sham: ★, $p < 0.01$; 3 d DC vs. sham: ★, $p < 0.05$; 14 d DC vs. sham: ★, $p < 0.05$).

neuronal loss in mice subjected to CCI without subsequent closure of skull defects (36). In a rat model, surgical decompression after FPI led to reduced brain edema formation with diminished AQP4 expression 48 h later (22). In CCI-treated rats, a positive effect of decompression (reduced volume of edema and contusion due to improved metabolic profile of the brain) was reported by Tian et al. up to 7d after trauma

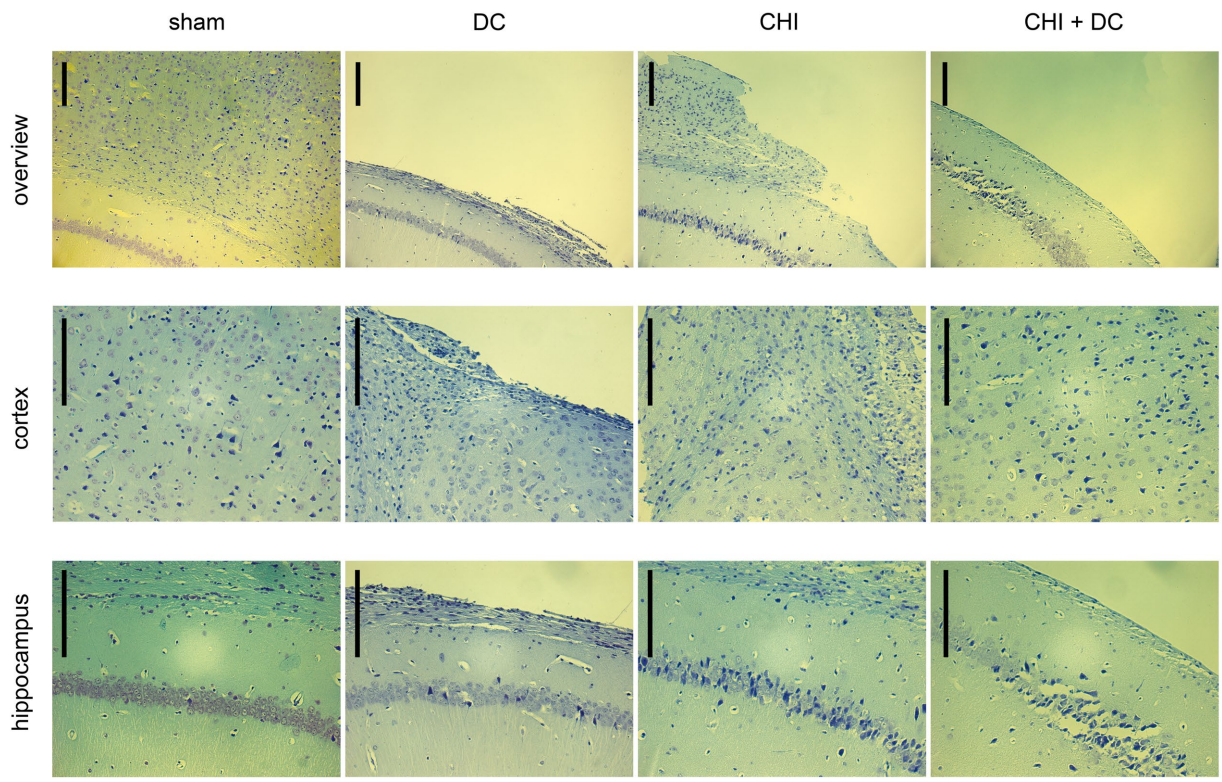

FIGURE 11
Photomicrographs of coronal paraffin sections obtained from animals subjected to sham treatment, decompressive craniectomy (DC), closed head injury (CHI), or closed head injury followed by DC (CHI + DC). All animals were sacrificed 28d postinjury. The sections were obtained from representative animals. Upper panel provides an overview of cortical layers (1-6b), subcortical structures (corpus callosum, alveus) and hippocampal CA1 area (striatum oriens, pyramidal layer and upper part of stratum radiatum), ipsilateral to injury site (magnification 100x, bar = 200 μm); middle row demonstrates cortex immediately adjacent the epicenter of injury (usually represented by defect of cortical brain tissue), layers 2/3 to 6b in greater magnification (200x, bar = 200 μm); bottom panel displays subcortical structures (corpus callosum and alveus) including stratum oriens, pyramidal layer and stratum radiatum of hippocampus (CA1) in greater magnification (200x, bar = 200 μm). Description of findings in the main text; note the necrotic area, mostly prominent in CHI+DC animal.

(23). Using the same model, Hou et al. reported improvement of behavioral changes by decompression, probably due to reduced impairment of synaptic function (24).

Our results are different from previous reports. Previously, using the CHI-DC model, we observed increased water content 6 h postinjury and augmented brain edema formation 24 h after TBI, accompanied by impaired neurological function (27, 37) in mice subjected to decompression (38). These characteristics bring our concept closer to early works on craniectomy performed by Cooper et al. using a cold lesion model. A 7-fold increase in brain water content was observed if craniectomy was performed during the phase of brain edema development (39). Notably, this early observation and our conclusions are not far from clinical practice. Additional brain swelling may be noted in 25 to 51% of TBI patients after craniectomy (40–45), occasionally leading to severe displacement of brain tissue outside the skull boundaries (known as external herniation or brain fungation) (46, 47). Certainly, a small decompression size increases the risk of this phenomenon (48, 49). However, external herniation may occur even if the craniectomy is properly sized (50). This effect was demonstrated in our experiment, along with a gradual decline in brain tissue prolapse over time. Thus, our results are consistent with some clinical reports (51) underlining the translational potential of our model.

The main goal of the current study was to analyze the dynamics of posttraumatic changes. Both trauma and surgical decompression trigger a long-lasting change in the physiological steady state (3, 18, 52). On the one hand, DC offers several benefits: improved intracranial compliance (12, 13), increased brain perfusion (5, 53, 54) and optimized brain metabolism (14, 55–57). On the other hand, craniectomy carries the disadvantage of brain exposure to external barometric pressure (55, 58), decreased CSF flow (59) or mechanistic shearing forces affecting the brain tissue (40, 48, 49, 60). The patients' outcome is the net effect of both positive and negative events over time. Thus, not only the intensity but also the duration and timing of the given DC action must be considered. The best example here is the craniectomy effect on the ICP. In the DECRA trial, craniectomy was extremely effective against intracranial hypertension. As a result, DC was able to shorten the length of stay in the ICU, but this early effect did not positively influence the long-term outcome (16).

One of the strengths of our study is the depiction of brain edema evolution in MRI imaging. Similar to Tsenter et al. and Onyszchuk et al., we demonstrated a peak of hypointense changes at 24 h and their secondary decline thereafter, with gradual appearance of hyperintensive lesions, reaching a plateau at 14d (61, 62). We assumed that initial changes represent cytotoxic edema (7, 8, 63–67). The hyperintensive abnormalities are more difficult to interpret. On the

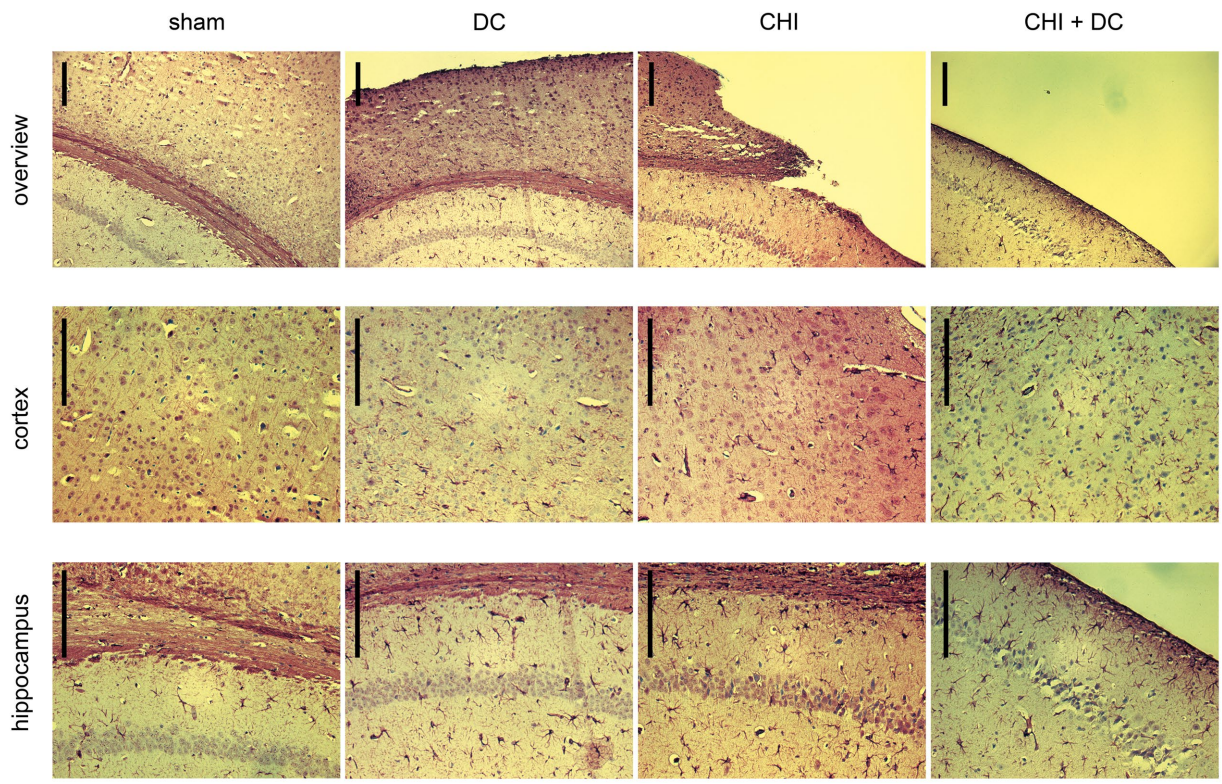

FIGURE 12
Photomicrographs of coronal paraffin sections obtained from animals subjected to sham treatment, decompressive craniectomy (DC), closed head injury (CHI), or closed head injury followed by DC (CHI + DC) and immunostained for GFAP. All animals were sacrificed 28d postinjury. The sections were obtained from representative animals. Similar to Figure 11, upper panel provides an overview of cortical layers (1-6b), subcortical structures (corpus callosum, alveus) and hippocampal CA1 area (striatum oriens, pyramidal layer and upper part of stratum radiatum), ipsilateral to injury site (magnification 100x, bar = 200 μm); middle row demonstrates cortex immediately adjacent the epicenter of injury (usually represented by defect of cortical brain tissue), layers 2/3 to 6b in greater magnification (200x, bar = 200 μm); bottom panel displays subcortical structures (corpus callosum and alveus) including stratum oriens, pyramidal layer and stratum radiatum of hippocampus (CA1) in greater magnification (200x, bar = 200 μm), description of findings in the main text.

one hand, vasogenic edema was present in various animal models of TBI (8, 68–71), including CHI (61, 72–74), and may manifest as ADC-hyperintensive areas (7, 68, 69, 74–76). On the other hand, their persistence (accompanied by T2-signal increase) suggests their gliotic or cavitary character (77, 78). Our histological analysis supports the latter interpretation, since we demonstrated the activation of astroglia and neuronal depletion resulting in tissue loss. Importantly, glial scarring has been described in other long-term rodent neurotrauma studies (79–82) and correlates with injury severity and functional outcome (83–88). Accordingly, in our interpretation, we demonstrated an early peak in cytotoxic edema, a secondary increase in vasogenic brain swelling and, finally, glial scar formation accompanied by neuronal loss 28d after TBI.

Most important observations were made in CHI+DC animals. Here, we demonstrated a significant impairment that was most prominent during the early posttraumatic phase. This pattern of functional improvement suits well the recovery potential seen in animal models of traumatic (24), ischemic (89, 90), or hemorrhagic brain injury (91) followed by surgical decompression. However, the prolonged negative effects of DC are specific to our model. One aspect is the evolution of cerebral swelling. From the very early time points, a massive increase in brain edema, accompanied by external herniation, could be observed. The main feature was the high volume of vasogenic edema, occurring earlier and more intensively than could be expected in the CHI model (61, 74). Here, the idea of increased water permeation from cerebral vessels to the brain parenchyma needs to be recalled. After craniectomy, vasogenic edema is no longer hampered by a rigid skull and may propagate freely (39, 92, 93). This effect may be accentuated by craniectomy-related changes in the expression of water channel proteins, such as aquaporin-4 (22, 33). Another consequence of pressure relief is the detamponade of contusional bleeding. The effect of hemorrhage blossoming after craniectomy is well recognized (46, 47, 50, 94, 95) and has been attributed to neurological deterioration in our short-term experiments (27) and in an animal model of subarachnoid hemorrhage (21). Finally, the negative impact of craniectomy on functional outcome may rely on shear load at the decompression rim (96), occurring while the progressive swelling is forcing the brain out of the cranial cavity (48, 49, 97). The decompressed brain may also suffer from chronic strains related to its deformation or to increased motility of the cerebral mass (98). This effect is potentially aggravated by changes in the mechanical properties of injured tissue (82, 99). This list of negative craniectomy effects needs to be kept in mind when discussing the unfavorable outcomes in the subset of

TBI patients represented in our study by the CHI+DC group. In a previous report, we documented a short-term edema surge and contusional blossoming after DC (27). Currently, we have described the time course of brain swelling after trauma and decompression. Based on these observations, we conclude that our experimental protocol favors the deleterious effects of decompression over the protective ones, differing in this matter from most animal craniectomy studies.

The postsurgical course in animals decompressed without prior TBI is of particular interest. After removing the skull covering, the brain is exposed to the caprices of external pressure (58). This potentially explains the brain tissue deformation (98). The negative effect of pressure changes has been recognized previously (100, 101) and may potentially justify some deleterious effects of craniectomy, including syndrome of the trephined (46, 102, 103). To mimic this effect, occurring in the treatment phase between decompressive craniectomy and skull reconstruction (cranioplasty) was one of the goals of our translational study. For this reason we have chosen the animal model, not requiring skull opening and subsequent closure for trauma application itself. Basen on this paradigm, we could make an observation that the procedure of decompression itself is not neutral. Even with the use of microsurgical techniques and meticulous prevention of thermal injury due to drilling, surgical procedures on the rodent skull are burdened by some negative effects, such as hemodynamic or metabolic depletion (104) and proinflammatory, morphologic and functional damage (105). The relevance of skull manipulation for the "true sham effect" has been postulated previously (105–107) and justifies the paradigm of using "sham decompressed" animals as a reference group in current and future series of experiments.

Our study is not free from limitations. Our data were provided in a limited number of subjects, as required by the general 3R principle (reduction-replacement-refinement) (108). Thus, the statistical power of our analysis is much less than that of multicenter randomized trials. Further, the established technique of surgical skull decompression in small rodent model is mimicking but not perfectly replicating the craniectomy performed in human patient. In particular the lacking step dura reconstruction after its incision (as usually performed in clinical condition) may theoretically exaggerate the impact of external pressure on the exposed brain. However, also in current clinical practice, the securing of dura by free overlay of tissue (or tissue substitute) is preferred over the traditional watertight closure (109).

The most important caveat regards the risk of overinterpretation of our data in the clinical context. Our results should not be directly extrapolated to humans, even if the concept of our experiment was translational. Our protocol refers to a very specific situation (primary decompression for severe, focal TBI), while TBI in the clinical setting is heterogeneous, and decompression is usually performed for secondary ICP increase (2, 110).

Conclusion

The main purpose of the study was to assess whether prolonged sequelae of decompressive craniectomy can be reproduced in experimental TBI and whether the effects of DC are persistent or transient. We demonstrated that decompressive craniectomy may accelerate the development of posttraumatic brain edema (in particular in its vasogenic form). The impact of skull decompression was not permanent and resolved over time. Two messages are important for clinical practice: The dynamics of posttraumatic brain edema are dramatically altered by skull decompression. Here, the cases of rapid malignant brain swelling with external herniation after decompression may be explained. Second, decompressive craniectomy after head trauma is the most dramatic but potentially not final form of treatment. We ought to seek brain edema therapies supplementary to surgical decompression.

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 Saarland University Hospital/ Saarland Ethical Commission. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

JS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. VH: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. EK: Formal analysis, Investigation, Methodology, Validation, Visualization, Data curation, Writing – review & editing. AM: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. LA: Data curation, Investigation, Validation, Visualization, Writing – review & editing. KS: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. JO: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work has been supported by financial award of voluntary association "Friends of Saarland University Medical Center" for JS.

Acknowledgments

We gratefully acknowledge the technical assistance of Sonja Hoffmann and Sigrid Welsch in experimental part of the study.

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.2023.1308683/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 12 December 2023
DOI 10.3389/fneur.2023.1308540

OPEN ACCESS

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RECEIVED 06 October 2023
ACCEPTED 23 November 2023
PUBLISHED 12 December 2023

CITATION
Eagle SR, Jain S, Sun X, Preszler J, McCrea MA, Giacino JT, Manley GT, Okonkwo DO, Nelson LD and The TRACK-TBI Investigators (2023) Network analysis and relationship of symptom factors to functional outcomes and quality of life following mild traumatic brain injury: a TRACK-TBI study. *Front. Neurol.* 14:1308540.
doi: 10.3389/fneur.2023.1308540

Network analysis and relationship of symptom factors to functional outcomes and quality of life following mild traumatic brain injury: a TRACK-TBI study

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Introduction: Mild traumatic brain injury (mTBI) is a heterogenous injury which can be difficult to characterize and manage. Using cross-sectional network analysis (NA) to conceptualize mTBI symptoms offers an innovative solution to identify how mTBI symptoms relate to each other. The centrality hypothesis of network theory posits that certain symptoms in a network are more relevant (central) or have above average influence over the rest of the network. However, no studies have used NA to characterize the interrelationships between symptoms in a cohort of patients who presented with mTBI to a U.S. Level 1 trauma center emergency department and how subacute central symptoms relate to long-term outcomes.

Methods: Patients with mTBI (Glasgow Coma Scale = 13–15) evaluated across 18 U.S. Level 1 trauma centers from 2013 to 2019 completed the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) at 2 weeks (W2) post-injury (n = 1,593) and at 3 months (M3), 6 months (M6), and 12 months (M12) post-injury. Network maps were developed from RPQ subscale scores at each timepoint. RPQ scores at W2 were associated with M6 and M12 functional and quality of life outcomes.

Results: Network structure did not differ across timepoints, indicating no difference in symptoms/factors influence on the overall symptom network across time. The cognitive factor had the highest expected influence at W2 (1.761), M3 (1.245), and M6 (1.349). Fatigue had the highest expected influence at M12 (1.275). The emotional factor was the only other node with expected influence >1 at any timepoint, indicating disproportionate influence of emotional symptoms on overall symptom burden (M3 = 1.011; M6 = 1.076).

Discussion: Several symptom factors at 2-weeks post-injury were more strongly associated with incomplete recovery and/or poorer injury-related quality of life at 6 and 12 months post-injury than previously validated demographic and clinical covariates. The network analysis suggests that emotional, cognitive, and fatigue symptoms may be useful treatment targets in this population due to high centrality and activating potential of the overall symptom network.

KEYWORDS
network analysis, mild traumatic brain injuries, trauma, symptoms, quality of life

Introduction

Mild traumatic brain injury (mTBI) continues to be a global public health concern. mTBI is a heterogenous injury across patients with significant variability in both short- and long-term outcomes (1, 2). There is a growing appreciation that mTBI can be linked to long-term consequences. For example, Nelson et al. (3) reported that 53% of mTBI patients evaluated at U.S. Level 1 trauma center emergency departments (EDs) report injury-related functional impairments 1-year post-injury. Functional impairments can have a direct impact on life quality and satisfaction and are often linked to persistent injury-related symptoms, such as psychological distress (3, 4).

Using network analysis (NA) to conceptualize post-mTBI symptoms offers an innovative solution to identify the interrelationships between a unique cohort's constellation of symptoms (5). In this framework, each node of the network corresponds to a specific symptom, while "edges" refer to the connections between nodes (i.e., symptoms) (6). NA theory suggests that a given pathology can be characterized as a dynamic relationship among active symptoms and produces a network map of the relationships between these symptoms, with the overall goal to identify individual symptoms or symptom clusters with particularly high influence on the overall network (7, 8). The centrality hypothesis of network theory posits that certain symptoms in an individual's network are more relevant or have above average influence over the rest of the network (9). For example, the "strength" (e.g., total number of connections for a symptom node) and expected influence, can be statistically compared. Researchers have suggested that targeting treatment to these central symptoms may improve overall symptom burden and reduce recovery time by shrinking the size of the network and reducing the role of the patient's most influential symptoms (5, 9). However, prior to initiating that type of NA (referred to as temporal network analysis) symptom network structure for patients with mTBI needs to be described at serial recovery timepoints.

Due to the reliance on subjective symptom reports to diagnose mTBI (in the absence of a positive head computed tomography [CT] scan), the relationship between mTBI symptoms has been described in a variety of populations and at different timepoints (7, 10–13). These studies typically use a type of factor analysis to understand the factor structure within the instrument, which is useful for identifying latent constructs which cluster together. However, no studies have used network analysis to characterize the interrelationships among symptoms in a cohort of community-acquired patients with mTBI diagnosed at a hospital ED. Moreover, our understanding of how post-acute symptomatology correlates with long-term functional outcomes and quality of life in mTBI patients who sought acute care at an ED is less complete in comparison to other populations (i.e., athletes, patients who first seek care at specialty clinics, etc.) (8, 12, 13). Patients who seek care from U.S. Level 1 trauma center EDs may have unique characteristics (e.g., high prevalence of positive head CT scans) that make findings from other TBI populations nongeneralizable given unique factors contributing to symptoms and long-term outcomes in this subpopulation.

We used network analysis to describe the interrelationship of mTBI symptoms across timepoints in the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) cohort. The primary aim of this study was to describe group-level symptom networks at 2 weeks, 3 months, 6 months, and 12 months post-mTBI, compare changes in network features over time, and identify the most central symptoms at each timepoint. The secondary aim was to evaluate the association of symptom factors at the two-week timepoint with function and quality of life measures at 6- and 12-months post-injury.

Methods

The current study is a retrospective cohort analysis of prospectively enrolled patients with mTBI who presented to the ED of 18 U.S. Level 1 trauma centers from 2013 to 2018. Participants or their legally authorized representatives provided written informed consent to participate after being approached by a member of the research team in the hospital. The Galveston Orientation and Amnesia Test (GOAT) was used, in part, to determine competency to self-consent. This study was approved for human subjects research by the institutional review board or ethics committee of each enrolling center.

Participants were included in the study if they presented to the hospital within 24 h of external force trauma to the head meeting the. American Congress of Rehabilitation Medicine's definition of TBI (14), as well as sufficient for the treating physician to order a head computed tomography (CT) scan. Exclusion criteria included pregnancy, incarceration, nonsurvivable physical trauma, debilitating mental health disorders or neurological disease, magnetic resonance imaging contraindications (for persons in the MRI cohort; e.g., cardiac pacemakers, aneurysm clips, insulin pumps), or any other reason the potential participant could not participate in a longitudinal study. Because the network analysis focused on mTBI, the sample was restricted to patients with a GCS score of 13 to 15 upon ED arrival with complete Rivermead Post-concussion Symptom Questionnaire (RPQ) assessments at 2 weeks (W2), 3 months (M3), 6 months (M6), and 12 months (M12) post-injury ($n = 1{,}059$). The secondary outcome analysis included GCS 13–15 patients with W2 RPQ and outcome scores M6 and M12 (Figure 1). The Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] reporting guideline.

Rivermead post concussion symptoms questionnaire (RPQ)

Participants completed the RPQ at W2, M3, M6, and M12. The 16-item RPQ measures severity of headaches, dizziness, and nausea as well as cognitive, mood, and sleep disturbances and other physical symptoms associated with mTBI. Each item is rated on a scale of 0 to

4 within the past 7 days, as compared with pre-injury status, with 0 indicating the symptom was not experienced at all, 1 indicating the symptom is no more of a problem, 2 indicating the symptom is a mild problem, 3 indicating the symptom is a moderate problem and 4 indicating the symptom was a severe problem (15). For analysis, each item was recoded as 0 = no problem or no more of a problem, 1 = mild problem, 2 = moderate problem, and 3 = severe problem the 0 and 1 options in the original RPQ reflect no substantive change in symptom burden.

Other clinical outcomes

Participants completed a standardized set of outcome assessments at W2, M3, M6, and M12, including the Glasgow Outcome Scale-Extended (GOSE), Short-Form 12 (SF-12), and the Quality of Life after Brain Injury (QOLIBRI-OS) Overall Scale. The QOLIBRI-OS is a health-related quality-of-life instrument used for TBI patients with six items that comprise an overall score (range 0–100, lower scores indicate worse quality of life) (16). The SF-12 is a brief survey of physical and mental health where lower scores correspond to worse self-reported health (17). The Glasgow Outcome Scale-Extended (GOSE) was used to assess functional outcome specific to TBI at W2, M3, M6, and M12 after injury. Complete recovery was defined as a GOSE score = 8; incomplete recovery was defined as GOSE <8.

Statistical analysis

Descriptive statistics were provided for the analysis cohort. Cross-sectional Gaussian graphical models (GGM) of RPQ symptoms were estimated using the graphical LASSO in combination with EBIC model selection and tuning parameter of 0.5 (18). This procedure required an estimate of a variance–covariance matrix to return a parsimonious network of partial correlation coefficients from which to begin our analyses. Preliminary network analysis revealed strong symptom clusters from the RPQ, where several symptoms (e.g., irritable with depressed and frustrated, poor memory with poor concentration and slow thinking, and blurred vision with light sensitivity and double vision) had uniquely strong relationships (edge weights = 0.29–0.46) with each other. Importantly, these clusters were consistent with prior work by Agtarap et al. (19) which found the symptoms in question formed second-order factors in the emotional, cognitive, and visual domains using exploratory and confirmatory factor analyses. This suggests the symptoms were measuring the same construct, and given network recommendations (20), the individual items within these domains were averaged into three composite variables that reflected Agtarap et al.'s findings (19) and were included as inputs in subsequent network analyses. The emotional composite was an average of irritable, depressed, and frustrated items; the cognitive composite was an average of poor memory, poor concentration, and slow thinking items; and the visual composite was an average of blurred vision, light sensitive, and double vision items. All other individual symptoms were entered as their own inputs.

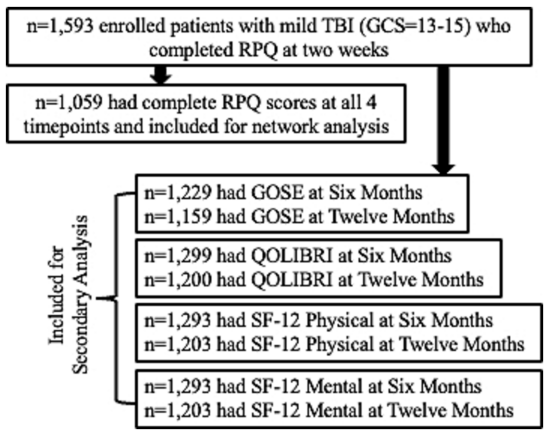

FIGURE 1
CONSORT diagram.

Network structure was plotted and expected influence of each node was estimated. Expected influence of each node was calculated for each timepoint, which indicates that node's importance in activating or deactivating other nodes in a network that has negative edges (9). Expected influence scores >1 were considered notable and indicative of high centrality (9).

The Network Comparison Test (NCT: van Borkulo et al. (21)) was used to statistically compare networks from different timepoints. Based on 1,000 permutations, we investigated network structure invariance (possible edge weight differences) and using family-wise Bonferroni corrections. Stability of node strength was evaluated by estimating network models based on subsets of the data using case-dropping bootstrap (6). Correlation Stability (CS) coefficient for correlation values equal or above to $r = 0.7$ were used to measure stability of centrality indices (22, 23). CS-coefficient indicates the percentage of our sample that can be dropped to maintain, with a 95% confidence interval, correlation values $(r) \geq 0.7$ between our sample's centrality indices and our bootstrapped samples' centrality indices (22).

Logistic regression models were used to study the association of W2 RPQ symptom factors with incomplete recovery (GOSE<8 vs. =8) at 6 and 12 months post-injury, adjusting for known risk factors, including demographics (age, sex, years of education), baseline clinical characteristics (prior TBI, psychiatric history), and CT status (positive or negative finding). To reduce the possibility of overfitting and preserve statistical power, symptoms were combined into factors as reported in prior work (19). The decision to analyze factors instead of individual symptoms was also consistent with the network modeling approach described above. In addition to the three factors discussed above, headache, dizziness, and nausea were combined into a somatic factor and noise sensitivity, sleep disturbance, fatigue, and restlessness were combined into an "other" factor. Odds ratio (OR) with 95% confidence interval was reported per unit increase in symptom factors. Similar linear regression models were built for QOLIBRI-OS, and the SF-12 Physical (PCS) and Mental Component scores (MCS). For these continuous outcome measures, beta coefficient with 95% confidence interval was reported. R (version 4.1.2) was used to complete all analyses.[1]

1 http://www.r-project.org

Results

Overall cohort

Characteristics of the overall cohort are presented in Table 1. The sample was age 40.6 ± 17.3 years old at time of injury and 66% male. ED arrival GCS was predominately 15 (77%), 18.5% had a GCS = 14, and 4.1% a GCS = 13, with 34.7% having a positive head CT. Only 49.2% of the sample achieved complete recovery (GOSE = 8) at M12.

Comparison of symptom networks over time

Networks over time appear in Figure 2. There was a statistically significant difference in network invariance between the W2 and M12 networks ($p = 0.026$). Post-hoc analysis revealed an absolute edge difference of 0.176 (Bonferroni-Holm corrected $p = 0.045$) between headache and nausea at W2 and M12. There was no statistically significant difference between networks at W2 and M3 ($p = 0.107$); W2 and M6 ($p = 0.65$); W2 and M12 ($p = 0.13$); M3 and M6 ($p = 0.06$); and M6 and M12 ($p = 0.18$). Network strength of edge weights was stable over time, with maximum drop in proportions of 0.517 (W2), 0.595 (M3 and M6), and 0.439 (M12).

Expected influence for each node is presented in Table 2. The cognitive factor had the highest expected influence at W2 (1.761), M3 (1.245) and M6 (1.349). Fatigue had the highest expected influence at M12 (1.275). The emotional factor was the only other node with expected influence >1 at any timepoint (M3 = 1.011; M6 = 1.076). Nausea had the lowest expected influence at all timepoints (−2.007 to −2.363).

Association of symptom factors at 2 weeks with functional and clinical outcomes at 6 months

Regression model outcomes at M6 can be viewed in Tables 3–6. Somatic (aOR = 1.84), other (aOR = 1.55), emotional (aOR = 1.39), and cognitive symptoms (aOR = 1.39) at 2 weeks were significantly associated with incomplete functional recovery (GOSE<8). Emotional ($\beta = -5.27$), cognitive ($\beta = -3.09$), other ($\beta = -3.58$), and visual symptoms ($\beta = -3.00$) at 2 weeks were significantly associated with lower QOLIBRI-OS scores. Other ($\beta = -2.45$) and somatic symptoms ($\beta = -1.51$) at 2 weeks were significantly associated with lower SF-physical scores. Emotional ($\beta = -2.72$), cognitive ($\beta = -1.40$), and visual ($\beta = -1.51$) symptoms at 2 weeks were significantly associated with lower SF-mental scores.

Association of symptom factors at 2 weeks with functional and clinical outcomes at 12 months

Regression model outcomes at 12 months can be viewed in Tables 3–6. Cognitive symptoms (aOR = 1.72) and other symptoms (aOR = 1.47) at 2 weeks were significantly associated with GOSE<8. Cognitive ($\beta = -5.18$), emotional ($\beta = -4.67$), and other ($\beta = -2.86$) symptoms at 2 weeks were significantly associated with lower QOLIBRI-OS scores. Other ($\beta = -2.24$), and cognitive ($\beta = -1.36$) symptoms at 2 weeks were significantly associated with lower SF-12 Physical scores. Emotional ($\beta = -2.20$) and cognitive ($\beta = -1.75$) symptoms at 2 weeks were significantly associated with lower SF-12 Mental scores.

TABLE 1 Participant characteristics and outcomes.

Age (n = 1,593)	40.6 ± 17.3
Male sex (n = 1,593)	1,055 (66.2)
Race (n = 1,585)	
White	1,224 (77.2)
Black	268 (16.9)
Other	93 (5.9)
Hispanic (n = 1,588)	329 (20.7)
Years of education (n = 1,560)	13.6 ± 2.9
Psychiatric history (n = 1,592)	353 (22.2)
GCS (n = 1,593)	
13	65 (4.1)
14	295 (18.5)
15	1,233 (77.4)
CT+ (n = 1,550)	538 (34.7)
GOSE at 6 months (n = 1,224)	
8	513 (41.9)
7	379 (31.0)
6	230 (18.8)
5	85 (6.9)
≤4	17 (1.4)
GOSE at 12 months (n = 1,159)	
8	570 (49.2)
7	319 (27.5)
6	184 (15.9)
5	73 (6.3)
≤4	13 (1.1)
QOLIBRI-OS at 6 months (n = 1,299)	66.25 ± 24.76
QOLIBRI-OS at 12 months (n = 1,200)	67.58 ± 24.97
SF Physical health at 6 months (n = 1,293)	47.40 ± 10.26
SF Physical health at 12 months (n = 1,293)	48.08 ± 10.09
SF Mental health at 6 months (n = 1,293)	48.46 ± 11.00
SF Mental health at 12 months (n = 1,293)	48.79 ± 11.01

Mean ± SD was reported for continuous variables; N (%) was reported for categorical variables.

Discussion

In this study of a large national cohort of participants diagnosed with mTBI at U.S. Level 1 trauma centers, centrality metrics were able to identify that emotional and cognitive symptoms exert an outsized

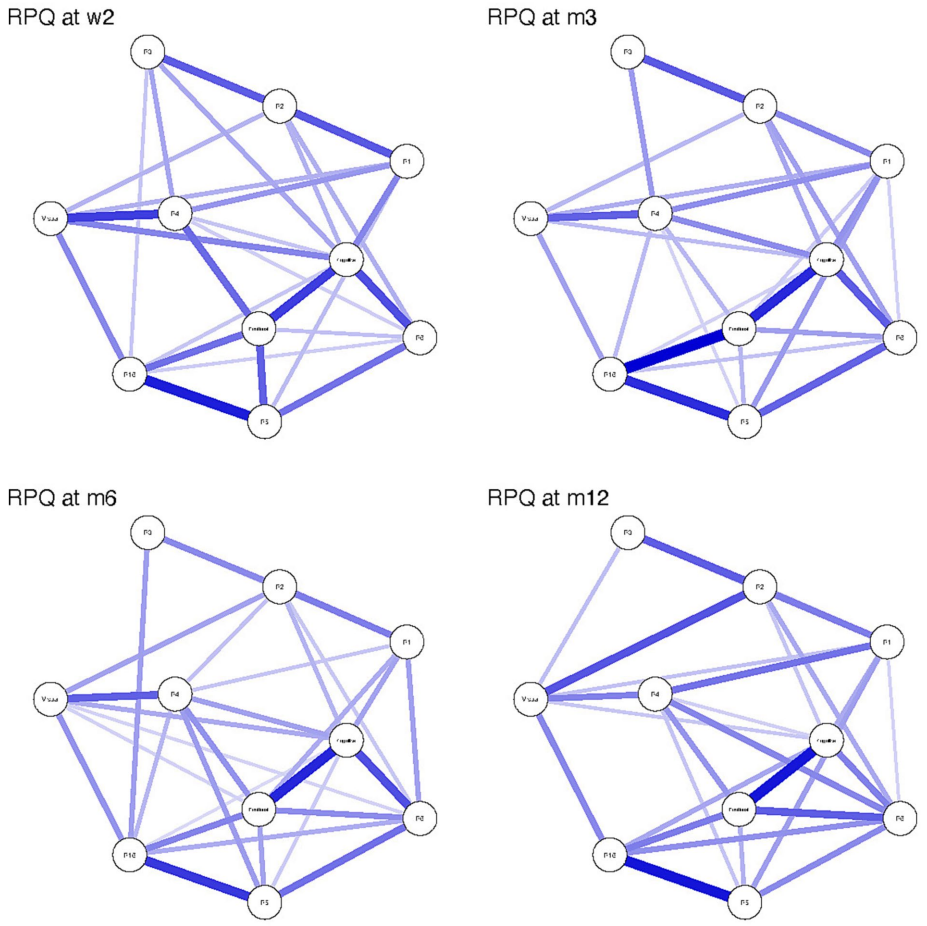

FIGURE 2
Rivermead Post-concussion Questionnaire (RPQ) symptom network structure at 2 weeks (W2), 3 months (M3), 6 months (M6) and 12 months (M12) following mild traumatic brain injury. Strength of the connection between nodes is illustrated by the thickness and darkness of the connecting edge, where thicker and darker edges mean higher strength of connection. R1 = headache, R2 = dizziness, R3 = nausea, R4 = noise sensitivity, R5 = Sleep disturbance, R6 = fatigue and R16 = restlessness.

TABLE 2 **Expected influence values for each node across timepoints.**

	Week 2	Month 3	Month 6	Month 12
Emotional	0.885	1.011	1.076	0.790
Cognitive	1.761	1.245	1.349	0.613
Visual	−0.225	−0.868	−0.551	−0.243
Headache	−0.688	0.069	−0.512	0.322
Dizziness	−0.497	−0.434	−0.561	−0.393
Nausea	−2.007	−2.152	−2.065	−2.363
Noise sensitivity	0.276	0.393	0.207	−0.227
Sleep disturbance	−0.157	−0.133	−0.201	−0.331
Fatigue	0.276	0.046	0.597	1.275
Restless	0.375	0.822	0.661	0.558

*a positive expected influence > 1 was suggestive of high centrality.

influence on other symptoms at several timepoints. In prior work with this population, Agtarap et al. (19) used exploratory and confirmatory factor analyses to characterize the RPQ and concluded that the RPQ is largely unidimensional. That result was consistent with prior work using a similar model structure with the global symptom checklist from the Sport Concussion Assessment Tool (SCAT) in a population of athletes with acute mTBI (13). Agtarap et al. (19) found that a bifactor model comprising an overarching general factor with three secondary factors (emotional, cognitive and visual) best fit the overall data and remained stable over time. The present study confirms those results, finding no differences in network structure over time and noting strong correlations among the symptoms that comprise the emotional, cognitive, and visual factors. Apart from a slight difference in the relationship between nausea and headache at 2 weeks compared with month 12 of recovery, network structure did not differ across timepoints.

After collapsing the individual symptoms of the above factors for network analyses, the results indicate that cognitive symptoms (i.e., forgetfulness, poor concentration, and taking longer to think) were the most influential to network structure at 2 weeks, 3 months, and 6 months post-injury. Higher expected influence of these nodes suggests that higher symptom scores for this factor could activate connected nodes (Table 2). For example, the cognitive composite was strongly associated with the emotional factor and fatigue (edge weights >0.2; Figure 1) indicating that these symptoms likely

co-activate each other. Within the context of a cross-sectional network, which was used in the present study, we cannot determine which symptoms directly cause activation of connected symptoms (i.e., whether emotional symptoms cause cognitive symptoms in this study, or vice versa). Emotional symptoms (i.e., feeling frustrated, irritable, depressed) had slightly lower expected influence scores at 3 and 6 months post-injury but their values likely reflect a similar role within the broader network (Table 2). The centrality of these two symptom factors suggests targeting treatments to these specific domains may "deactivate" the network and reduce overall symptom burden. Future studies need to employ temporal network analyses to delineate cause and effect of early symptom burdens on chronic symptoms, which could provide the basis for identifying useful treatment targets in the ED population with mTBI.

Another key finding from the present study is the principal role subacute symptom burden (i.e., at 2 weeks post-injury) plays in predicting worse functional outcomes and quality of life at 6 and 12 months. Consistently, a single symptom factor carried the first or second strongest association to each long-term outcome, after controlling for known covariates, highlighting the importance of understanding how subacute symptom burden can influence long-term function (24). It is also important to note that certain factors were more relevant to specific long-term domains than others, and this relationship may vary based upon time. For example, somatic symptoms (i.e., headaches, dizziness, nausea) were the primary predictor of incomplete recovery (GOSE<8) and a significant predictor of worse physical health scores at 6 months but were not significantly associated to any other long-term outcome. Pre-injury somatization and high post-injury somatization is a known risk factor for prolonged recovery from sport-related concussion in younger populations (25–27), but less is known about the role of somatic symptoms following mTBI in adults. Nelson et al. found that higher acute somatic symptoms contributed to a prediction model of longer symptom burden for both patients with mTBI and other trauma (28). In a small

TABLE 3 Logistic regression models predicting incomplete recovery (GOSE<8 vs. =8) at 6 months (left; $n = 1{,}172$) and 12 months (right; $n = 1{,}114$) from demographics, head CT findings, and two-week symptoms.

Six months				Twelve months		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Emotional	1.39	1.07–1.81	0.013*	1.08	0.84-1.39	0.551
Cognitive	1.39	1.10–1.77	0.007*	1.72	1.37-2.18	<0.0005*
Visual	1.02	0.73-1.43	0.904	1.33	0.96–1.85	0.088
Somatic	1.84	1.38–2.46	<0.0005*	1.26	0.95-1.66	0.106
Other symptoms	1.55	1.14–2.10	0.005*	1.47	1.09-1.99	0.011*
Age	1.01	1.00-1.02	0.01*	1.01	1.00-1.02	0.003*
Female sex	0.92	0.68–1.24	0.592	1.18	0.87–1.60	0.286
Years of education	0.92	0.88–0.97	0.002*	0.86	0.82-0.91	<0.0005*
Prior TBI	1.13	0.84–1.51	0.426	1.23	0.91–1.65	0.179
Psychiatric history	1.34	0.96–1.86	0.083	1.35	0.97–1.88	0.077
CT+	1.48	1.11–1.97	0.008*	1.73	1.29-2.32	<0.0005*

*statistically significant difference between groups at $p < 0.05$.

TABLE 4 Linear regression models for QOLIBRI-OS at 6 (left; $n = 1{,}248$) and 12 months (right; $n = 1{,}158$).

	Six months			Twelve months		
	β	95%CI	*p*	β	95%CI	*p*
Emotional	−5.27	−7.36, −3.18	<0.0005*	−4.67	−6.90, −2.45	<0.0005*
Cognitive	−3.09	−5.09, −1.10	0.002*	−5.18	−7.24, −3.11	<0.0005*
Visual	−3.00	−5.43, −0.57	0.016*	−0.62	−3.17, 1.93	0.635
Somatic	−1.80	−4.13, 0.53	0.129	−1.74	−4.20, 0.72	0.164
Other symptoms	−3.58	−6.11, −1.04	0.006*	−2.86	−5.53, −0.20	0.035*
Age	−0.20	−0.27, −0.13	<0.0005*	−0.18	−0.25, −0.11	<0.0005*
Female sex	0.64	−1.93, 3.21	0.625	1.69	−1.00, 4.38	0.219
Years of education	0.98	0.56, 1.41	<0.0005*	1.37	0.92, 1.82	<0.0005*
Prior TBI	−3.50	−6.04, −0.96	0.007*	−4.19	−6.86, −1.52	0.002*
Psychiatric history	−10.55	−13.40, −7.70	<0.0005*	−10.06	−13.06, −7.05	<0.0005*
CT+	1.06	−1.48, 3.60	0.413	0.96	−1.69, 3.62	0.476

*statistically significant difference between groups at $p < 0.05$.

sample of patients with mTBI recruited from a level 1 trauma center, Stubbs et al. (29) reported higher somatic symptoms in patients with complete recovery (GOSE = 8) than patients with incomplete recovery (GOSE<8). The role of somatic symptoms in recovery from mTBI in adults may warrant future investigation as a potentially modifiable risk factor for recovery at 6 months.

An interesting temporal trend was also observed for the cognitive symptom factor, such that their importance in relation to long-term outcomes seemed to increase from 6 to 12 months. Cognitive symptoms at 2 weeks were significantly associated with higher odds of incomplete recovery, worse quality of life, and worse mental health at 6 months post-injury (Tables 3–6). However, the strength of the association between cognitive symptoms and these outcomes increased at 12 months post-injury. Further, cognitive symptoms went from a non-significant predictor at 6 months to the second strongest predictor of SF-12 Physical health at 12 months (Table 5). Why the association between cognitive symptoms and SF-12 physical health strengthened between six and 12 months post-mTBI is unknown. More research is needed to better understand the role of subjective cognitive complaints following mTBI, especially in relation to long-term outcomes, as cognitive complaints could exist relative to the individual's prior performance that may not be detectable with neurocognitive testing.

The "other" symptom factor (i.e., sleep disturbance, fatigue, noise sensitivity, and restlessness) was associated with incomplete recovery at 6 (aOR = 1.55) and 12 months (aOR = 1.47) and had the strongest association of all predictors with worse physical health at 6 and 12 months (Table 5). In the network analysis, fatigue at 12 months was the only individual symptom with an expected influence >1 at any timepoint, indicating it may be a useful treatment target. Fatigue is a common symptom following mTBI, occurring in 68% of patients at 1 week post-injury (30), and up to 1 in 3 patients experiences severe fatigue at 6 months post-injury (31). Sleep disturbances are also very common following mTBI, with roughly half of mTBI patients reporting sleep issues and 1 in 4 patients reporting a diagnosed sleep condition (e.g., sleep apnea, insomnia) (32). Despite the prevalence of these symptoms and their relationship to worse outcomes following TBI, very few randomized controlled trials have assessed the utility of interventions targeting these conditions (33). Dischinger et al. (34) reported that endorsing noise sensitivity between 3 and 10 days following mTBI after admission to a level 1 trauma center was associated with 3.1 times higher odds of post-concussion syndrome at 3 months. Noise sensitivity following mTBI appears to be mediated by fear avoidance behaviors (35), which are a possible treatment target for this population but little to no interventional studies addressing this issue exist (36).

There are limitations to this study. Symptoms by nature are self-reported and subject to bias. The networks presented are cross-sectional, so temporal relationships between symptoms could not be investigated. As such, no "cause and effect" conclusions could be made. The symptom factors were correlated with moderate strength ($r = 0.48$ to 0.70). This is common in mTBI symptom assessments due to the commonality of a pervading "general" symptom factor across these tools (12, 13, 19). As a result, the factors are not completely discrete from each other and significant relationships found between individual factors and other outcomes may not be exclusively related to the individual factor. These results are only generalizable to adult patients with mTBI who presented to a level 1 trauma center emergency department. It is not possible to discern the role of any potential treatments on the group-level networks presented, but future research quantifying the temporal effects of targeted treatments on network structure will be important.

Conclusion

In this longitudinal cohort study of patients diagnosed with mTBI at a level 1 trauma center emergency department, network analysis revealed emotional and cognitive symptom factors had the highest influence on the overall network from the subacute to chronic recovery periods. The network analysis suggests that emotional and cognitive symptoms may be useful treatment targets in this population due to high centrality and activating potential of the overall network (i.e., high expected influence). This finding needs to be validated by a temporal network analysis to determine cause and effect of these symptoms on later individual symptoms and overall network strength. When analyzed as symptom factors, reporting higher symptoms at 2 weeks were associated with higher odds of incomplete recovery and poorer quality of life at 6 and 12 months.

TABLE 5 Linear regression model for Short Form 12 Physical Health at 6- (left; $n = 1{,}241$) and 12-months (right; $n = 1{,}161$).

	Six months			Twelve months		
	β	95%CI	p	β	95%CI	p
Emotional	−0.325	−1.234, 0.583	0.482	−0.300	−1.237, 0.637	0.53
Cognitive	−0.867	−1.732, −0.002	0.05	−1.361	−2.232, −0.491	0.002*
Visual	−0.598	−1.646, 0.451	0.264	−1.064	−2.139, 0.011	0.052
Somatic	−1.510	−2.516, −0.505	0.003*	−0.439	−1.475, 0.596	0.406
Other symptoms	−2.449	−3.542, −1.355	<0.0005*	−2.242	−3.362, −1.122	<0.0005*
Age	−0.185	−0.215, −0.155	<0.0005*	−0.174	−0.204, −0.143	<0.0005*
Female sex	1.094	−0.013, 2.202	0.053	0.624	−0.510, 1.757	0.281
Years of education	0.674	0.491, 0.857	<0.0005*	0.714	0.525, 0.903	<0.0005*
Prior TBI	0.356	−0.739, 1.452	0.524	−0.534	−1.659, 0.592	0.353
Psychiatric history	−2.030	−3.260, −0.799	0.001*	−1.239	−2.503, 0.025	0.055
CT+	2.364	1.271, 3.456	<0.0005*	1.298	0.180, 2.416	0.023*

*statistically significant difference between groups at $p < 0.05$.

TABLE 6 Linear regression model for Short Form 12 mental health at 6- (left; $n = 1{,}241$) and 12-months (right; $n = 1{,}161$).

	Six months			Twelve months		
	β	95%CI	p	β	95%CI	p
Emotional	−2.715	−3.685, −1.745	<0.0005*	−2.196	−3.238, −1.155	<0.0005*
Cognitive	−1.399	−2.323, −0.475	0.003*	−1.746	−2.714, −0.778	<0.0005*
Visual	−1.510	−2.631, −0.390	0.008*	0.455	−0.740, 1.649	0.456
Somatic	0.109	−0.965, 1.184	0.842	−0.737	−1.888, 0.413	0.209
Other	−0.906	−2.074, 0.263	0.129	−0.597	−1.841, 0.648	0.347
Age	0.009	−0.023, 0.041	0.573	0.012	−0.022, 0.046	0.499
Female sex	−0.836	−2.020, 0.347	0.166	−0.108	−1.368, 1.152	0.866
Years of education	0.081	−0.114, 0.277	0.415	0.357	0.147, 0.566	0.001*
Prior TBI	−1.908	−3.078, −0.737	0.001*	−2.175	−3.426, −0.924	0.001*
Psychiatric history	−5.008	−6.324, −3.693	<0.0005*	−5.004	−6.408, −3.599	<0.0005*
CT+	−0.286	−1.454, 0.881	0.631	−0.260	−1.502, 0.982	0.681

*statistically significant difference between groups at $p < 0.05$.

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 each institution (the full list is available as a Supplementary file). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SE: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. SJ: Data curation, Formal analysis, Methodology, Writing – review & editing. XS: Data curation, Formal analysis, Methodology, Writing – review & editing. JP: Methodology, Writing – review & editing. MM: Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. JG: Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. GM: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. DO: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. LN: Conceptualization, Methodology, Project administration, Writing – review & editing.

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Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the National Institutes of Health (award number: 1U01NS086090–01).

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.2023.1308540/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Brief Research Report
PUBLISHED 04 January 2024
DOI 10.3389/fneur.2023.1329042

OPEN ACCESS

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RECEIVED 27 October 2023
ACCEPTED 14 December 2023
PUBLISHED 04 January 2024

CITATION
Generoso E, Diep C, Hua C, Rader E, Ran R, Lee NJ and Rivera-Lara L (2024) Assessing risk factors associated with breakthrough early post-traumatic seizures in patients receiving phenytoin prophylaxis.
Front. Neurol. 14:1329042.
doi: 10.3389/fneur.2023.1329042

Assessing risk factors associated with breakthrough early post-traumatic seizures in patients receiving phenytoin prophylaxis

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Objective: Post-traumatic seizure (PTS) is a well-known complication of traumatic brain injury (TBI). The objective of this study was to identify risk factors associated with breakthrough early PTS in TBI patients receiving phenytoin prophylaxis.

Methods: This was a single-centered retrospective study including adult patients admitted to the intensive care unit (ICU), had a TBI, and started on phenytoin for seizure prophylaxis within 24 h of admission. The primary outcome was the incidence and factors associated with early PTS, defined as a confirmed seizure on a continuous electroencephalogram within 7 days of TBI. Secondary outcomes included the association between early post-traumatic seizures and ICU length of stay, hospital length of stay, and in-hospital mortality.

Results: A total of 105 patients were included in the final analysis. Patients with early PTS were older (65 vs. 48 years old, $p = 0.01$), had a higher Marshall score (5 vs. 2, $p = 0.01$), were more likely to have a Marshall score > 2 (73 vs. 37%, $p = 0.01$), and had more neurosurgeries for hematoma evacuation (57 vs. 19%, $p = 0.01$). In patients with early PTS, 57% had a level at the time of seizure, and of those, 87.5% had a therapeutic level (>10 mcg/mL). Patients with early PTS had a longer ICU length of stay (14.7 vs. 5.9 days, $p = 0.04$) and a greater proportion of hospital mortality (21 vs. 2%, $p = 0.02$).

Conclusion: Patients with higher age, Marshall score, and neurosurgical procedures for hematoma evacuation had higher incidences of breakthrough early PTS despite the use of phenytoin prophylaxis. The majority of patients with early PTS had therapeutic phenytoin levels at the time of seizure when a level was available; however, approximately half (43%) did not have a level.

KEYWORDS

traumatic brain injury, post-traumatic epilepsy, phenytoin, risk factors, seizure prophylaxis

1 Introduction

Post-traumatic seizure (PTS) is a well-known complication of traumatic brain injury (TBI) resulting in long-term impairment, disability, and reduced quality of life (1, 2). Currently, there is mixed evidence and consensus regarding the safety and efficacy of phenytoin for PTS prophylaxis (3–6). The Brain Trauma Foundation guidelines recommend phenytoin for 7 days following severe TBI to prevent early seizures (within 7 days of injury; Level IIA recommendation) (3). Some trials have also shown no benefit and potential harm including longer hospital stays and worse functional outcomes at discharge with the use of antiepileptic drugs (AEDs) for early PTS prophylaxis, though many are limited by retrospective designs (7–11). Risk factors for early PTS include Glasgow Coma Scale (GCS) score of <10; immediate seizures; PTS amnesia lasting >30 min; linear or depressed skull fracture; penetrating head injury; subdural, epidural, or intracerebral hematoma; cortical contusion; or chronic alcoholism; however, these are often identified in patients not receiving prophylactic AEDs (12, 13). Finally, greater than 60% of early PTS occur despite having therapeutic phenytoin levels (7, 8). The purpose of this study was to identify factors associated with breakthrough early PTS in TBI patients receiving phenytoin for seizure prophylaxis. This study also aimed to describe phenytoin monitoring practices for PTS prophylaxis given the limited guidance in the literature.

2 Methods

2.1 Study design and study population

This was a single-center, retrospective study conducted at Stanford Health Care (SHC), an academic level 1 trauma center, between January 1, 2010 and March1, 2023. Patients were included if they were 18 years or older, admitted to the intensive care unit (ICU), had an International Classification of Diseases (ICD) 9 or 10 code for TBI, and started on phenytoin for seizure prophylaxis within 24 h of admission for at least 6 days or until the first hospital seizure. Patients were excluded if they had a history of seizure, were on AEDs prior to admission, received concomitant AEDs while on phenytoin prophylaxis, had a reported seizure without confirmation on continuous electroencephalogram (cEEG), transitioned to comfort care within 7 days of admission, incarcerated, or pregnant.

2.2 Ethical approval

This study protocol was approved by the Stanford Institutional Review Board (IRB no. 66917, approved September 2, 2022). This study was conducted in accordance with the ethical standards of the Stanford IRB and with the Helsinki Declaration of 1975. For this study, formal consent was not required.

2.3 Study outcomes and definitions

The primary outcome was to examine the incidence and factors associated with early PTS, defined as a confirmed seizure on cEEG within 7 days of TBI documented by a neurologist in the electronic medical record (EMR). Data were extracted via chart review of the EMR. Admission computerized tomography (CT) imaging was reviewed by a neuroradiologist and a neurologist, blinded to outcomes, to calculate the Marshall score (definitions in Supplementary material) (14). Electrographic seizure was defined as epileptiform discharges averaging >2.5 Hz for ≥10 s (>25 discharges in 10 s), or any pattern with definite evolution and lasting ≥10 s (15). Electrographic status epilepticus was defined as electrographic generalized seizures for ≥5 continuous minutes, and focal status epilepticus was defined as electrographic focal seizures for ≥10 continuous minutes. The cEEG was interpreted by the on-called epileptologist and was categorized based on documentation in the neurology notes. Secondary outcomes included the association between early PTS and ICU length of stay, hospital length of stay, and in-hospital mortality.

Severe TBI patients are primarily managed by the trauma/surgical ICU team in consultation with the neurology team when the primary team deems it necessary. The use of cEEG is generally not a standard practice for all TBI patients at SHC. Continuous EEG monitoring is often initiated once a seizure is suspected or for unexplained encephalopathy and is at the discretion of the consulting neurocritical care and neurology team.

Initiation and dosing of phenytoin for early PTS prophylaxis was at the discretion of the treating team. Phenytoin monitoring and dose adjustments were also managed by the treating team. Phenytoin levels (mcg/mL) were corrected for hypoalbuminemia and renal dysfunction using the closest albumin and serum creatinine result preceding the phenytoin level (corrected phenytoin = measured phenytoin level/[(adjustment × albumin, g/dL) + 0.1], adjustment = 0.275; in patients with creatinine clearance <20 mL/min, adjustment = 0.2) (16). Appropriately drawn phenytoin maintenance level was defined as a level drawn 6–8 h following a phenytoin dose to reflect a trough level (17, 18).

2.4 Statistical analysis

IBM SPSS Statistics 22 (IBM Analytics, Armonk, NY, United States) was used to perform all statistical analyses with a predefined significance level of 0.05 by two-tailed asymptotic or exact tests. Parametric continuous variables were compared using ANOVA. Non-parametric continuous variables were analyzed using the Mann–Whitney U-test, and categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test. The relationship between seizures and age, Marshall score, number of neurosurgical procedures, and hematoma evacuation were further explored using univariate binary logistic regression. The low event rate for seizures precluded a single large multivariate binary logistic regression. Instead, bivariate binary logistic regression was performed on seizures vs. hematoma evacuation and age as well as seizures vs. Marshall score > 2 and age.

3 Results

A total of 197 patients were screened for inclusion. The most common reason for exclusion was seizure history on AEDs prior to admission ($n = 54$; see Figure 1). Of the remaining patients, 105 were

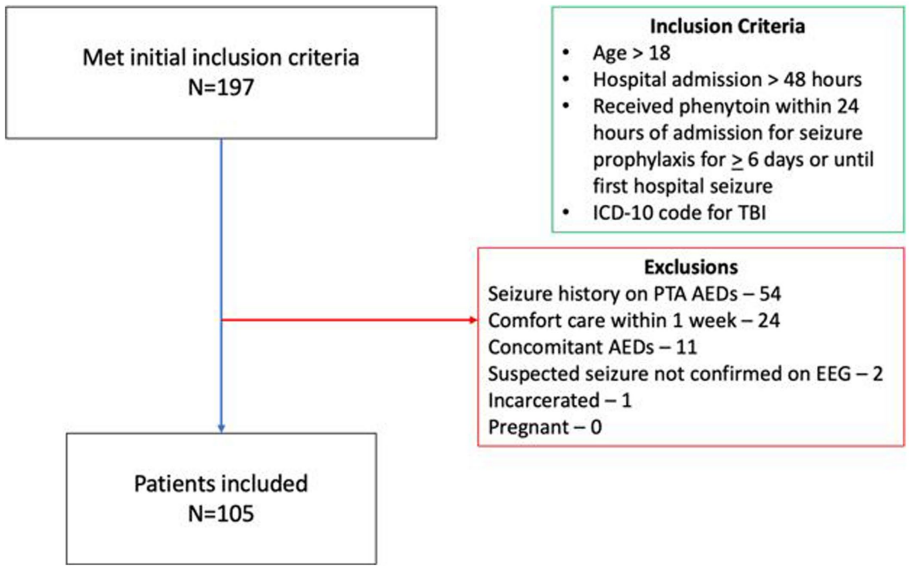

FIGURE 1
Patient inclusion/exclusion flow chart. ICD, International classification of diseases; TBI, Traumatic brain injury; PTA, Prior to admission; AED, Anti-epileptic drug; and EEG, Electroencephalogram.

included in the final analysis, 14 had early PTS, and 91 did not. Patients who had early PTS were older (65 vs. 48 years old, $p = 0.01$), had a higher Marshall score (5 vs. 2, $p = 0.01$), a greater proportion of patients with Marshall score > 2 (73 vs. 37%, $p = 0.01$), underwent more neurosurgeries for hematoma evacuation (57 vs. 19%, $p = 0.01$), and a higher number of neurosurgical procedures (1 vs. 0, $p = 0.02$). The average time from hospital admission to the first reported seizure on cEGG was 2.8 days in patients who had early PTS. Concomitant gabapentin use was more frequent in patients without early PTS (26 vs. 0%, $p = 0.04$). Patient characteristics are shown in Table 1.

Appropriately drawn phenytoin levels (level drawn 6–8 h after a phenytoin dose) were available in 55% of patients with no early PTS vs. 79% of patients with early PTS ($p = 0.19$). The duration of phenytoin prophylaxis was shorter in the early PTS group (2.5 vs. 7 days, $p < 0.01$). In patients with early PTS, 57% had a level at the time of seizure, and of those, 87.5% had a therapeutic level (>10 mcg/mL). Phenytoin level and dosing data are shown in Table 2.

Univariate regression analysis showed that the following were associated with early PTS: Age (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.01–1.07, $p = 0.01$), Marshall score (OR 1.7, 95% CI 1.15–2.61, $p = 0.02$), Marshall score > 2 (OR 6.4, 95% CI 1.68–24.77, $p = 0.01$), and hematoma evacuation (OR 5.8, 95% CI 1.78–18.94, $p = 0.02$). Regression analyses assessing risk factors associated with early PTS are shown in Supplementary Tables 2–4.

The early PTS group had a longer ICU length of stay (14.7 vs. 5.9 days, $p = 0.04$) and a greater proportion of hospital mortality (21 vs. 2%, $p = 0.02$). Secondary outcomes are shown in Table 3. Of patients who experienced early PTS, 93% were focal and 7% were generalized seizures. Epileptiform activity on cEEG as noted by the neurology note was categorized as status epilepticus (36%), clinical (7%), or subclinical seizures (57%). Seizure data are shown in Supplementary Table 1.

4 Discussion

In this study including critically ill patients with TBI receiving phenytoin for seizure prophylaxis, older age, higher Marshall score, Marshall score > 2, and neurosurgery for hematoma evacuation were associated with breakthrough early PTS. This study showed that patients with these characteristics seized despite receiving phenytoin prophylaxis and the majority having therapeutic phenytoin levels.

There are currently limited studies that investigate risk factors for breakthrough early PTS in patients receiving prophylactic AEDs. Majidi et al. (19) found that seizures occurred more frequently in patients with old age, African American ethnicity, moderate TBI, history of alcohol dependence, and subdural hematoma. However, the choice of AED used for PTS prophylaxis as well as the description of dosing and levels are limited. A *post-hoc* exploratory analysis found that hematoma evacuation and Marshall score > 2 were associated with early PTS occurrence after adjusting for age. Higher severity of injury (GCS < 10) and hematoma evacuation have also been found to be associated with early PTS in TBI patients not receiving pharmacologic seizure prophylaxis (12, 20, 21). Given the current literature and our findings, closer monitoring and aggressive AED dosing may be considered in patients with these characteristics.

Antiepileptic drug dosing and achieving effective target levels play a vital role in determining the efficacy of AEDs for preventing early PTS. There are limited recommendations regarding phenytoin monitoring as well as data on the relationship between therapeutic phenytoin levels and a rate of early PTS. A total serum phenytoin concentration of 10–20 mcg/mL is a widely accepted target range to prevent seizures, but this has not been confirmed (22). Retrospective and randomized studies in patients with severe TBI have reported that 60–100% of patients who experience early PTS have therapeutic phenytoin levels (7, 8). Similarly, 87.5% of patients in this study had a therapeutic phenytoin level when a level was available at the time of seizure occurrence. The high occurrence of early PTS despite having

TABLE 1 Patient characteristics for patients with and without early post-traumatic seizures.

	No seizure ($n = 91$)	Seizure ($n = 14$)	p value
Age (years), mean ± SD	48 ± 20	65 ± 21	**0.01**
Male, *n* (%)	68 (75%)	11 (79%)	1
BMI, mean ± SD	25 ± 7	24 ± 4	0.60
Admission GCS, median (IQR)	13 (7–14)	11.5 (8–14)	0.88
Marshall score, median (IQR)	2 (2–4)	5 (3–5)	**0.01**
Marshall score > 2, *n* (%)	34 (37)	11 (73)	**0.01**
ETOH ≥50 mg/dL, *n* (%)	17 (19%)	2 (14%)	1
Positive toxicology screen, *n* (%)	26 (29%)	4 (29%)	1
Amphetamine	6 (7%)	1 (7%)	1
Benzodiazepine	12 (13%)	1 (7%)	0.69
Cocaine	2 (2%)	1 (7%)	0.35
Opioids	8 (9%)	1 (7%)	1
THC	14 (15%)	1 (7%)	0.69
Mechanical ventilation, *n* (%)	59 (65%)	12 (80%)	0.22
Vasopressor use, *n* (%)	32 (35%)	8 (57%)	0.14
Hyperosmolar therapy, *n* (%)	52 (57%)	12 (86%)	0.07
Hypertonic saline	34 (37%)	9 (64%)	
Mannitol	2 (2%)	0 (0%)	
Both	16 (18%)	3 (21%)	
Concomitant injuries, *n* (%)	90 (99%)	14 (100%)	1
Subarachnoid hemorrhage	70 (77%)	9 (67%)	0.33
Subdural hematoma	54 (59%)	11 (79%)	0.24
Epidural hematoma	13 (14%)	1 (7%)	0.69
Intraventricular hemorrhage	14 (15%)	5 (36%)	0.13
Intraparenchymal hemorrhage	39 (43%)	7 (50%)	0.77
Depressed skull fracture	13 (14%)	1 (7%)	0.69
Cortical contusion	38 (42%)	6 (43%)	1
Diffuse axonal injury	10 (11%)	1 (7%)	1
Penetrating injury	1 (1%)	2 (14%)	0.05
Immediate seizure (within 24 h)	2 (2%)	1 (7%)	0.35
Number of concomitant injuries, median (IQR)	3 (2–4)	3 (3–4)	0.21
Number of neurosurgery procedures, median (IQR)	0 (0–1)	1 (1–2)	**0.02**
Neurosurgery procedure, *n* (%)	41 (45%)	11 (79%)	**0.02**
External ventricular drain	23 (25%)	4 (29%)	0.75
Bolt	4 (4%)	1 (7%)	0.52
Decompressive craniotomy	18 (20%)	5 (36%)	0.18
Hematoma evacuation	17 (19%)	8 (57%)	**0.01**
Prior to admission medications, *n* (%)			0.14
Antipsychotics	2 (2%)	1 (7%)	
Benzodiazepines	1 (1%)	0 (0%)	
Both	0 (0%)	1 (7%)	
Concomitant medications, *n* (%)			
Gabapentin	24 (26%)	0 (0%)	**0.04**
Scheduled benzodiazepine	8 (9%)	2 (14%)	0.62
Propofol infusion >48 h	17 (19%)	3 (21%)	0.73
Midazolam infusion >48 h	0 (0%)	1 (7%)	1
Time from admission to first seizure on cEEG (days), mean (SD)	NA	2.8 (1.6)	NA

BMI, Body mass index; ETOH, Ethanol; GCS, Glasgow Coma Scale; IQR, Interquartile range; SD, Standard deviation; THC, Tetrahydrocannabinol; cEEG, Continuous electroencephalogram; and NA, Not applicable. Bold values indicate statistically significant values $p < 0.05$.

TABLE 2 Phenytoin level and dosing data for patients with and without early posttraumatic seizures.

	No seizure (n = 91)	Seizure (n = 14)	p value
Phenytoin levels description, n (%)			0.19
At least one appropriate maintenance level drawn[a]	50 (55%)	11 (79%)	
Subtherapeutic	15 (16%)	3 (21%)	
Therapeutic/supratherapeutic[b]	35 (38%)	8 (57%)	
No appropriate maintenance level drawn	21 (23%)	3 (21%)	
No maintenance level drawn	20 (22%)	0 (0%)	
Loading dose given, n (%)	67 (74%)	12 (86%)	0.51
Loading dose (mg/kg), mean ± SD	18.3 ± 5.3	17.2 ± 3.6	0.48
Initial total daily dose (mg), mean ± SD	300 ± 0	300 ± 0	1
Average total daily dose (mg), median (IQR)	300 (300–300)	300 (271–300)	0.59
Duration of phenytoin prophylaxis (days), median (IQR)	7 (6.55–7.85)	2.5 (1.6–4)	**<0.01**
Number of levels during first 7 days, median (IQR)			
Inappropriate levels	1 (0–4)	2 (1–3)	0.69
Appropriate levels	1 (0–2)	2 (1–3)	**0.04**
Dose titration, n (%)			0.27
None	71 (78%)	7 (50%)	
Increase	11 (12%)	4 (29%)	
Decrease	4 (4%)	3 (21%)	
Both increase/decrease	3 (3%)	0 (0%)	
Bolus	2 (2%)	0 (0%)	
Time to first therapeutic level (days), median (IQR)[c]	1.3 (0.7–2.7)	1.9 (1.4–4.3)	0.09
Average level during first 7 days (mcg/mL), mean ± SD	12.3 ± 5.6	13.2 ± 6.6	0.67
% time in therapeutic range, median (IQR)[d]	100 (0–100)	86 (33–100)	0.09
Phenytoin level at time of seizure[e], n (%)			NA
No level	NA	6 (43%)	
Available level	NA	8 (57%)	
Subtherapeutic (< 10 mcg/mL)	NA	1 (12.5%)	
Therapeutic/supratherapeutic (≥ 10 mcg/mL)	NA	7 (87.5%)	

IQR, Interquartile range; SD, Standard deviation. [a]Phenytoin levels were categorized as appropriately drawn if drawn 6–8 h after a dose. [b]Patients were categorized as having therapeutic/supratherapeutic levels if greater than 50% of appropriately drawn levels within the first 7 days of injury were > 10 mcg/mL. [c]Based on patients with > 1 therapeutic level: no seizure (N = 35); seizure (N = 8). [d]Only for patients with > 1 appropriate maintenance level drawn; no seizure (N = 50), seizure (N = 14). [e]Available level preceding seizure event. Bold values indicate statistically significant values $p < 0.05$.

TABLE 3 Secondary outcome results in patients with and without early post-traumatic seizures.

	No seizure (n = 91)	Seizure (n = 14)	p value
In hospital seizure after 7 days, n (%)	1 (1%)	0 (0%)	1
ICU length of stay (days), median (IQR)	5.9 (3.2–13.7)	14.7 (5–21.9)	0.04
Hospital length of stay (days), median (IQR)	11.9 (8.4–24)	20.6 (12.3–28.9)	0.09
Hospital mortality, n (%)	2 (2%)	3 (21%)	0.02

ICU, Intensive care unit; IQR, Interquartile range.

therapeutic phenytoin levels may indicate that the traditional target level of 10–20 mcg/mL is suboptimal and/or there is a subset of patients with a high epileptogenic focus that is not tempered by phenytoin alone. The average phenytoin level at the time of seizure was 17.1 mcg/mL. It is unclear whether alternative AEDs or multiple AEDs for these higher-risk patients would be effective. Based on the results of this study, higher vigilance in patients with these risk factors and possibly an alternative AED may be considered keeping in mind that efficacy is also unclear. Further studies are warranted to determine the optimal phenytoin target and AED for preventing early PTS as well as if there is a subgroup of severe TBI that will benefit more than others.

The incidence of early PTS after severe TBI while on prophylactic phenytoin ranges from 3 to 4% based on randomized and retrospective studies (5–7, 22–24). In this study, the incidence of early PTS was higher at 13%. These differences are likely due to the study population, severity of TBI, use of concomitant medications with anti-epileptic properties, phenytoin dosing, co-management of these patients with neurocritical care, and the use of a cEEG. This study only included patients admitted to the ICU with admissions >6 days; 99% had at least one type of brain injury on CT imaging, and 60% received hyperosmolar therapy. Based on the results of this study, patients with a Marshall score > 2, older age, and/or neurosurgical procedures for hematoma evacuation had higher incidences of breakthrough PTS; determining the optimal prophylactic AED regimen is key to reducing PTS incidences.

The other consideration is that AED prophylaxis could be ineffective for early PTS. Though guidelines recommend phenytoin for early seizure prophylaxis following severe TBI, there is currently mixed evidence regarding the efficacy of AEDs for preventing PTS. Temkin et al. found that phenytoin reduced the rate of early PTS compared to placebo (3.6 vs. 14.2%, $p < 0.001$) in a single-centered randomized trial in patients with severe TBI (5). Young et al. (7) found that phenytoin did not reduce the incidence of early PTS in patients with severe TBI with over 78% of patients with phenytoin levels >10 mcg/mL at days 1, 3, and 7 after injury. Several retrospective studies have also found no difference in the rate of early PTS in patients who received AED for prophylaxis including phenytoin, levetiracetam, or valproic acid compared to patients who received no AEDs (8–10). The mixed results could be attributed to the varying definitions of severe TBI across randomized trials as well as the varying severity of TBI included in retrospective studies. It is possible that prophylactic AED is ineffective as several studies suggest; however, there may be a subset of patients that may benefit that have yet to be identified.

There were several limitations to this study including its single-centered retrospective nature and the potential confounders inherent to such a design. Overall, 22% of patients did not have maintenance phenytoin levels drawn and 22% of patients had levels drawn inappropriately. In addition, in patients with early PTS, 43% did not have a level at the time of seizure and it is possible that these patients had subtherapeutic levels which may have led to seizure occurrence. However, this reflects a real-world practice as levels may not be drawn correctly or not drawn at all. Free phenytoin levels may be more accurate in the acute care setting. However, free phenytoin level is a send out lab with a 3-day turnaround time and is not commonly used for phenytoin monitoring at SHC. Instead, corrected phenytoin levels were used and reported, which is a common alternative when free phenytoin levels are not readily available. It is also difficult to pinpoint the relationship between seizure occurrence and therapeutic phenytoin levels as levels are often drawn once a day, leaving the possibility that breakthrough seizures may occur during an uncaptured time when phenytoin levels are subtherapeutic. Data regarding intravenous (IV) versus enteral phenytoin use were not collected; however, patients were typically started on IV phenytoin and transitioned to enteral phenytoin to complete the 7-day prophylactic course at the discretion of the primary team. Patients with early PTS had a shorter phenytoin duration due to switching to a different AED once a seizure occurred. Patients were categorized as having seizures only if this was confirmed on a cEEG, which may underestimate the number of seizures. The use of gabapentin, which may have anti-epileptic properties though relatively weak, was more frequent in the no PTS group compared to the PTS group. Patients with more severe TBI and PTS generally do not have an indication for gabapentin, while gabapentin is often used to manage neuropathic pain and/or alcohol withdrawal in patients with less severe TBI. Other AEDs have been studied for early PTS prophylaxis; however, these agents were not included in this study. Despite a higher proportion of early PTS observed in this study, the absolute number of PTS was low; this limited the ability to conduct robust multivariate analysis to identify independent risk factors for early PTS.

This study showed that patients with a higher Marshall score, age, and neurosurgical procedures for hematoma evacuation had higher incidences of breakthrough early PTS despite the use of phenytoin prophylaxis. The majority of patients had therapeutic phenytoin levels at the time of PTS. Further studies are warranted to confirm factors associated with breakthrough early PTS and to determine the optimal monitoring and therapeutic phenytoin targets to prevent early PTS.

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 studies involving humans were approved by Stanford Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

EG: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. CD: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. CH: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. ER: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. RR: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. NL: Data curation, Writing – original draft. LR-L: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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.2023.1329042/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 12 January 2024
DOI 10.3389/fneur.2023.1338545

OPEN ACCESS

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RECEIVED 14 November 2023
ACCEPTED 27 December 2023
PUBLISHED 12 January 2024

CITATION
Tang J, Zhong Z, Nijiati M and Wu C (2024) Establishment and external validation of a nomogram for predicting 28-day mortality in patients with skull fracture.
Front. Neurol. 14:1338545.
doi: 10.3389/fneur.2023.1338545

Establishment and external validation of a nomogram for predicting 28-day mortality in patients with skull fracture

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Background: Skull fracture can lead to significant morbidity and mortality, yet the development of effective predictive tools has remained a challenge. This study aimed to establish and validate a nomogram to evaluate the 28-day mortality risk among patients with skull fracture.

Materials and methods: Data extracted from the Medical Information Mart for Intensive Care (MIMIC) database were utilized as the training set, while data from the eICU Collaborative Research Database were employed as the external validation set. This nomogram was developed using univariate Cox regression, best subset regression (BSR), and the least absolute shrinkage and selection operator (LASSO) methods. Subsequently, backward stepwise multivariable Cox regression was employed to refine predictor selection. Variance inflation factor (VIF), akaike information criterion (AIC), area under the receiver operating characteristic curve (AUC), concordance index (C-index), calibration curve, and decision curve analysis (DCA) were used to assess the model's performance.

Results: A total of 1,527 adult patients with skull fracture were enrolled for this analysis. The predictive factors in the final nomogram included age, temperature, serum sodium, mechanical ventilation, vasoactive agent, mannitol, extradural hematoma, loss of consciousness and Glasgow Coma Scale score. The AUC of our nomogram was 0.857, and C-index value was 0.832. After external validation, the model maintained an AUC of 0.853 and a C-index of 0.829. Furthermore, it showed good calibration with a low Brier score of 0.091 in the training set and 0.093 in the external validation set. DCA in both sets revealed that our model was clinically useful.

Conclusion: A nomogram incorporating nine features was constructed, with a good ability in predicting 28-day mortality in patients with skull fracture.

KEYWORDS

skull fracture, head trauma, prognosis, nomogram, prediction model

Introduction

A skull fracture denotes the breakage of one or more bones within the skull vault or base, typically resulting from road traffic accidents, falls, or acts of violence. Head injuries are more commonly observed in middle- and low-income countries, particularly in the context of road traffic collisions (1). In a retrospective study involving 2,254 cases of head trauma caused by assault, approximately one-third of the patients were found to suffer from a skull fracture (2). The most prevalent skull fracture occurs at

the parietal bone, followed by the temporal, occipital, and frontal bones (3). Unlike fractures in other body parts, skull fracture, in the absence of injury to vital structures like brain tissue, are not immediately life-threatening and often heal spontaneously. However, severe skull fracture can lead to concomitant trauma-related intracranial injuries, such as cerebral edema, subarachnoid hemorrhage, and cerebral lacerations, resulting in prolonged hospitalization and increased treatment costs. Traumatic intracranial hemorrhage (tICH) is a significant source of morbidity and mortality in trauma patients. Subdural hematoma (SDH), occurring in 11% to 49% of patients after traumatic brain injury (TBI), is commonly associated with an all-cause mortality rate of 14.2% to 53.8% within a five-year period (4).

Compared to TBI, skull fractures can be diagnosed both earlier and more easily, offering a more direct point for assessment and intervention. The development of a severity scoring system that accounts for mortality risk is imperative to accurately evaluate the prognosis and guide treatment strategies for patients with skull fracture. It not only aids in the early identification of patients with potentially fatal skull fractures but also optimizes resource distribution and patient management, particularly in emergency medical settings.

In recent years, there has been an upsurge in studies focusing on nomograms pertaining to head injuries. Nomograms offer an intuitive graphical representation, enhancing the comprehension and application of complex mathematical models and statistical methods. Healthcare professionals can expeditiously calculate individual risks by directly interpreting the variables and scales depicted in the chart (5). Chen et al. (6) formulated a predictive nomogram for assessing mortality in TBI patients, incorporating eight features (mannitol use, mechanical ventilation, vasopressor use, international normalized ratio, urea nitrogen, respiratory rate, and cerebrovascular disease). Lin et al. (7) developed a model to predict post-traumatic epilepsy (PTE) after cerebral contusions using seven variables [contusion site, chronic alcohol use, contusion volume, skull fracture, subdural hematoma (SDH), Glasgow coma scale (GCS) score, and non-late post-traumatic seizure], and the model exhibited excellent performance with a C index exceeding 0.9.

However, to the best of our knowledge, there currently exists no predictive model for assessing 28-day mortality in critically ill patients diagnosed with skull fracture. This study utilized two large public databases, namely the Medical Information Mart for Intensive Care (MIMIC) database and eICU Collaborative Research Database (eICU-CRD), to systematically screen predictive factors for 28-day mortality of critically ill patients with skull fracture. Subsequently we constructed a nomogram and ensured its validation. This model can be utilized by medical practitioners to enhance clinical decision-making, accurately anticipate mortality rates, and reduce uncertainty.

Materials and methods

Data source

Our data were sourced from the MIMIC-IV database (version 2.0), MIMIC-III Clinical Database CareVue subset (version 1.4) and eICU-CRD (version 2.0). MIMIC is a substantial, single-center, openly accessible database. It encompasses data from 2001 to 2019 within the intensive care units (ICUs) at Beth Israel Deaconess Medical Center. The eICU database is a multi-center database comprising health data associated with over 200,000 admissions to ICUs across the United States between 2014 and 2015. Rigorous de-identification measures have been applied to patient identity and hospital information in both databases. After successfully completing the training courses stipulated by the National Institutes of Health (NIH) and passing the relevant examination, we were granted permission to extract data. The first author of this study, Jia Tang, has completed the Collaborative Institutional Training Initiative (CITI) program courses and executed the data use agreement, thereby obtaining full access to the aforementioned two databases (record ID: 52759164).

Research population

All patients with skull fracture from the two databases were included in this study. For patients with multiple ICU admission, only data from the initial ICU admission were considered. None of the participants in our research were minors, and we exclusively enrolled individuals with a minimum ICU duration of 24 h. The Structured Query Language (SQL) queries used for the selection of patients with skull fracture are presented in Supplementary Table S1.

Feature extraction

We extracted the following data: age, sex, race, vital signs, laboratory data and Glagow Coma Scale (GCS) within 24 h after ICU admission (heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, hemoglobin, white blood cell count, platelet, prothrombin time, sodium, potassium, bicarbonate, serum creatinine); therapeutic interventions in the first 24 h (mechanical ventilation, vasoactive agent, furosemide, mannitol, human serum albumin, antibiotics); surgery for fracture; comorbidities (hypertension, chronic obstructive pulmonary disease, congestive heart failure, liver cirrhosis, cancer), fracture site (vault, base), open fracture, closed fracture, hemorrhage (subarachnoid hemorrhage, subdural hematoma, extradural hematoma), cerebral laceration and contusion, concussion, loss of consciousness. Additionally, we incorporated the acute physiology score III (APSIII), a widely employed tool for accessing disease severity. In this study, vasoactive agents included dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, vasopressin, and milrinone. Antibiotic users did not encompass those who administered antibiotics nasally or ocularly, nor did they include individuals using antibiotic creams or gels. Surgical data pertained to whether surgical operations were conducted during hospitalization due to skull fracture. The primary endpoint for this research was mortality within 28 days following ICU admission. Any variable with missing data exceeding 20% was removed from the analysis. Missing values for all variables were imputed by multiple imputation method (8). All requested information was

obtained using Navicat 16 for PostgreSQL through Structured Query Language (SQL).

Statistical analysis

Data from the MIMIC-IV databse and MIMIC-III carevue subset served as the training set and underwent 10-fold cross-validation, while data from eICU-CRD were used for external validation. The Shapiro-Wilk normality test was applied to all continuous variables. For normally distributed variables, the mean and standard deviation (SD) were utilized, while non-normally distributed variables were represented as the median and interquartile range (IQR). Categorical variables were expressed as numerical values and percentages (%). The distinction between two groups was evaluated using the *t* test or Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. Statistical significance was determined with a two-sided $P < 0.05$. R software (version 4.3.1) and MedCalc (version 22.009) were employed to perform the statistical analyses.

Model development phase

In the initial screening for significant prognostic factors, we employed three methods: univariate Cox regression, best subset regression (BSR), and least absolute shrinkage and selection operator (LASSO). In the univariate Cox model, factors with a $P < 0.05$ were included in subsequent analysis. The BSR method evaluated all possible variable combinations and selected final variables based on the maximum value of adjusted R^2. LASSO regression determined variable selection based on the lambda.1se value. Subsequently, each of the three models underwent backward stepwise multivariate Cox regression for secondary screening of independently significant factors. Ultimately, the akaike information criterion (AIC) and receiver operating characteristic (ROC) curves were employed to identify the optimal model, leading to the construction of a nomogram. Any variable that contradicted established clinical knowledge was eliminated. We calculated the variance inflation factor (VIF) to ensure no collinearity among the selected covariates (collinearity was considered when VIF > 4.0). Additionally, we checked whether the nomogram adhered to the "10 EPV" guideline (9), which stipulates that the number of positive samples should be at least ten times the number of predictive variables.

For internal validation section, we employed 200 rounds of 10-fold cross validation to assess the model performance. The discrimination of the nomogram was assessed using the area under the receiver operating curve (AUC) and concordance index (C-index). The AUCs of the three models were compared using the DeLong's test. We assessed the consistency between the nomogram-predicted and actual outcomes using a calibration curve generated through bootstrapped resampling (1,000 iterations) and the Brier

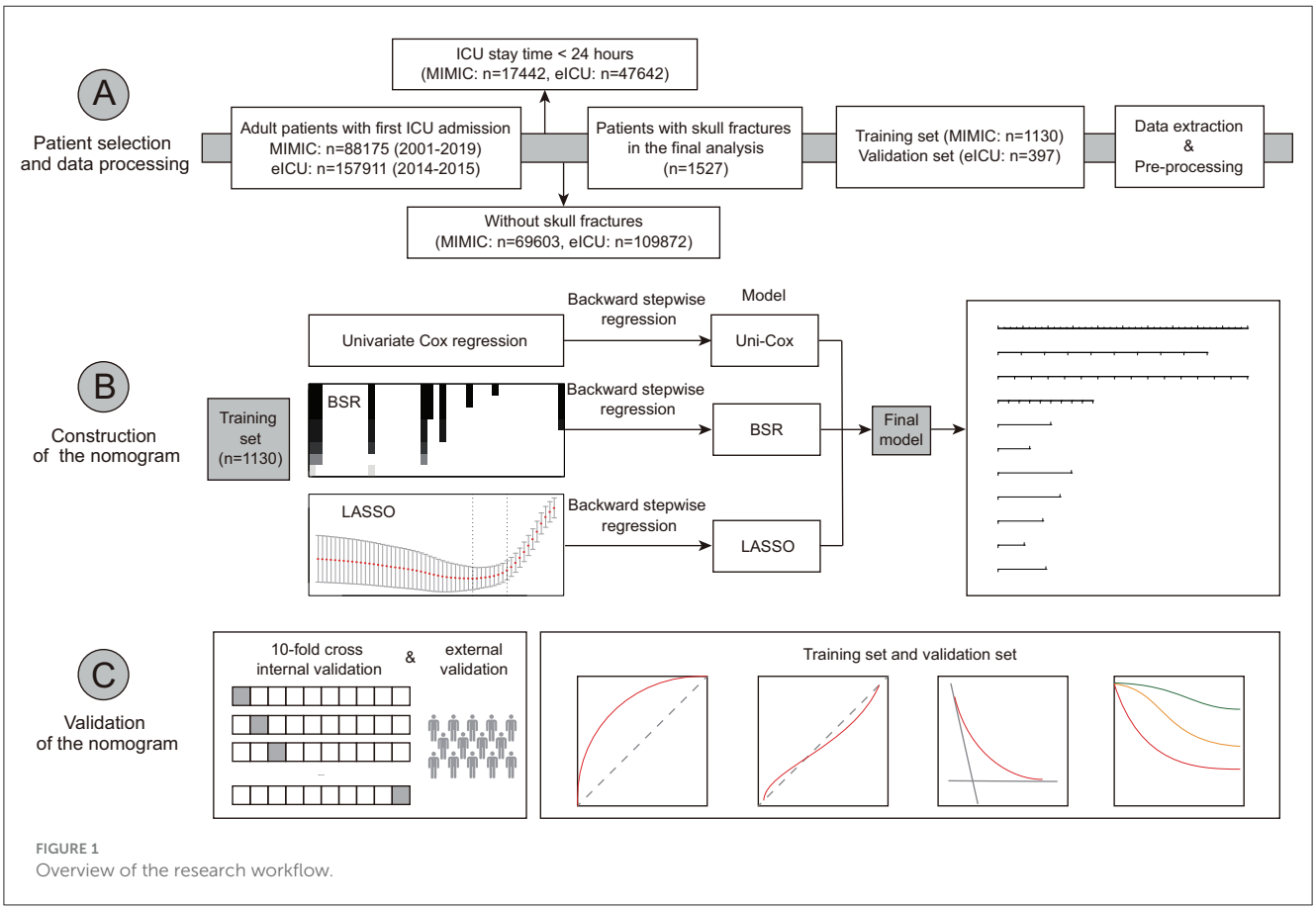

FIGURE 1
Overview of the research workflow.

TABLE 1 Demographic and clinical characteristics of the training and validation sets.

Variables	Total	Training set	Validation set	*P* value
	$n = 1,527$	$n = 1,130$	$n = 397$	
Age[a]	50.43 [30.19, 67.64]	52.16 [31.18, 67.89]	44.00 [28.00, 65.00]	0.001
Female[b]	424 (27.8)	330 (29.2)	94 (23.7)	0.040
Race[b]				<0.001
White	997 (65.3)	677 (59.9)	320 (80.6)	
Black	55 (3.6)	26 (2.3)	29 (7.3)	
Others	475 (31.1)	427 (37.8)	48 (12.1)	
Vital signs[a]				
Heart rate, bpm	86.00 [73.00, 100.00]	86.00 [73.00, 99.00]	86.00 [71.00, 102.00]	0.829
SBP, mmHg	131.00 [115.00, 146.00]	131.00 [115.00, 144.00]	134.00 [116.00, 148.00]	0.030
DBP, mmHg	71.00 [61.00, 83.00]	70.00 [60.00, 81.00]	77.00 [65.00, 89.00]	<0.001
Respiratory rate, bpm	18.00 [15.00, 21.00]	18.00 [15.00, 21.00]	18.00 [16.00, 21.00]	0.928
Temperature, °C	36.78 [36.31, 37.21]	36.83 [36.33, 37.22]	36.70 [36.28, 37.00]	<0.001
Laboratory results[a]				
Hb, g/dL	13.20 [11.60, 14.40]	12.90 [11.40, 14.20]	13.60 [12.10, 14.80]	<0.001
WBC, 10^9/L	13.20 [9.70, 17.50]	13.30 [9.80, 17.80]	12.80 [9.30, 17.00]	0.128
Platelet, 10^9/L	225.00 [182.00, 277.00]	226.00 [182.00, 280.00]	223.00 [182.00, 264.00]	0.278
PT, s	12.80 [11.70, 13.90]	12.60 [11.60, 13.50]	13.50 [12.20, 14.50]	<0.001
Sodium, mmol/L	140.00 [137.00, 142.00]	140.00 [137.00, 142.00]	139.00 [137.00, 141.00]	0.163
Potassium, mmol/L	3.90 [3.60, 4.30]	3.90 [3.60, 4.30]	3.80 [3.50, 4.20]	<0.001
Bicarbonate, mmol/L	23.00 [20.00, 25.00]	23.00 [20.00, 25.00]	23.00 [21.00, 26.00]	0.019
SCr, mg/dL	0.90 [0.70, 1.10]	0.90 [0.70, 1.10]	0.90 [0.73, 1.10]	0.108
Therapeutic interventions[b]				
MV	862 (56.5)	661 (58.5)	201 (50.6)	0.008
Vasoactive agent	255 (16.7)	218 (19.3)	37 (9.3)	<0.001
Furosemide	57 (3.7)	54 (4.8)	3 (0.8)	<0.001
Mannitol	169 (11.1)	138 (12.2)	31 (7.8)	0.021
HSA	36 (2.4)	34 (3.0)	2 (0.5)	0.008
Antibiotics	708 (46.4)	651 (57.6)	57 (14.4)	<0.001
Surgery for fracture[b]	167 (10.9)	133 (11.8)	34 (8.6)	0.095
Comorbidities[b]				
Hypertension	404 (26.5)	325 (28.8)	79 (19.9)	0.001
COPD	25 (1.6)	17 (1.5)	8 (2.0)	0.646
CHF	73 (4.8)	10 (2.5)	63 (5.6)	0.020
Liver cirrhosis	27 (1.8)	23 (2.0)	4 (1.0)	0.265
Cancer	37 (2.4)	24 (2.1)	13 (3.3)	0.274
Fracture site[b]				
Vault of skull	342 (22.4)	253 (22.4)	89 (22.4)	1.000
Base of skull	851 (55.7)	783 (69.3)	68 (17.1)	<0.001
Fracture feature[b]				
Open fracture	106 (6.9)	83 (7.3)	23 (5.8)	0.352

(Continued)

TABLE 1 (Continued)

Variables	Total	Training set	Validation set	*P* value
	n = 1,527	*n* = 1,130	*n* = 397	
Closed fracture	1,101 (72.1)	1,039 (91.9)	62 (15.6)	<0.001
Hemorrhage[b]				
Subarachnoid hemorrhage	892 (58.4)	716 (63.4)	176 (44.3)	<0.001
Subdural hematoma	908 (59.5)	730 (64.6)	178 (44.8)	<0.001
Extradural hematoma	601 (39.4)	566 (50.1)	35 (8.8)	<0.001
Cerebral laceration and contusion[b]	181 (11.9)	137 (12.1)	44 (11.1)	0.644
Concussion[b]	38 (2.5)	22 (1.9)	16 (4.0)	0.035
Loss of consciousness[b]	787 (51.5)	729 (64.5)	58 (14.6)	<0.001
GCS (point)[a]	13.00 [7.00, 15.00]	13.00 [9.00, 15.00]	8.00 [3.00, 14.00]	<0.001

[a]Expressed as median [IQR]; [b]expressed as n (%).
IQR, interquartile range; bpm, beats/breaths per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; WBC, white blood cell count; PT, prothrombin time; SCr, serum creatinine; MV, mechanical ventilation; HSA, human serum albumin; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; GCS, Glasgow Coma Scale.

score (ranging from 0 to 1, with 0 indicating perfect calibration). Decision curve analysis (DCA) was conducted to exhibit the clinical usefulness of the nomogram. Using the nomogram, we calculated total points for each patient and performed risk stratification using the X-tile (version 3.6.1) software (10). This categorization divided patients into low, mid, and high-risk groups. The survival outcomes of three groups were analyzed using Kaplan-Meier survival curves and evaluated by log-rank test.

Results

Patient characteristics

This study included a total of 1,527 records of critically ill patients with skull fractures, comprising 1,130 patients from the MIMIC database and 397 patients from the eICU database (Figure 1). Supplementary Figures S1, S2 showed that the proportion of all missing values in two groups was less than 20%. No statistical significance was observed in the data, either before or after imputation (Supplementary Tables S2, S3). Moreover, there was no statistically significant difference between training set and external validation set in terms of heart rate, respiratory rate, WBC, platelet, sodium, serum creatinine, surgery for fracture, COPD, liver cirrhosis, cancer, open fracture, and cerebral laceration and contusion (Table 1). Patients in the training set had older age [52.16 (95% CI: 31.18–67.89) vs. 44.00 (95% CI: 28.00–65.00), $P = 0.001$], higher body temperature [36.83 (95% CI: 36.33–37.22) vs. 36.70 (95% CI: 36.28–37.00), $P < 0.001$], a higher mechanical ventilation use rate [661 (58.5%) vs. 201 (50.6%), $P = 0.008$], a higher vasoactive agent use rate [218 (19.3%) vs. 37 (9.3%), $P < 0.001$], a higher mannitol use rate [138 (12.2%) vs. 31 (7.8%), $P = 0.021$], a higher extradural hematoma rate [566 (50.1%) vs. 35 (8.8%), $P < 0.001$] than those in the external validation set. The GCS score in the training set was also higher.

Construction of the nomogram

In the initial stage, 22 significant (defined as factors with P values less than 0.05) features (age, DBP, temperature, Hb, WBC, bicarbonate, platelet, PT, sodium, liver cirrhosis, SCr, MV, vasoactive agent, furosemide, mannitol, congestive heart failure, base fracture, subarachnoid hemorrhage, subdural hematoma, extradural hematoma, loss of consciousness, and GCS) were selected through univariate Cox hazard analysis (Figure 2). Using the maximum value of adjusted R^2 (value: 8) from BSR, we identified eight variables (age, temperature, MV, vasoactive agent, mannitol, sodium, liver cirrhosis, and loss of consciousness) (Figure 3). Additionally, four variables (age, temperature, mv, and vasoactive agent) were selected through LASSO regression using the lambda.1se value (Figure 4). Subsequently, we conducted a backward stepwise multivariable Cox regression analysis on the variables of each model to identify factors with $P < 0.01$ (Table 2). Considering the importance of GCS for neurological disorders and its ease of accessibility, we have additionally added this parameter to each model, even though it was eliminated in the statistical screening process. We compared the AIC and AUC values among three models (Figure 5). In the uni-Cox model (nine variables: age, temperature, sodium, MV, vasoactive agent, mannitol, extradural hematoma, loss of consciousness and GCS score), the AIC was 2073.121 and AUC was 0.857 (95% CI: 0.827–0.886); in the BSR model (nine variables: age, temperature, sodium, MV, vasoactive agent, mannitol, liver cirrhosis, loss of consciousness and GCS score), the AIC was 2075.264 and AUC was 0.861 (95% CI: 0.832–0.889); in the LASSO model (five variables: age, temperature, mv, vasoactive agent, and GCS), the AIC was 2132.724 and AUC was 0.838 (95% CI: 0.807–0.868). The AUC of the uni-Cox model was significantly different from the LASSO model (DeLong's test: $P = 0.019$), but there was no significant difference between the uni-Cox model and BSR model (DeLong's test: $P = 0.328$). Moreover, the uni-Cox model achieved the highest sensitivity at 81.5%, with the BSR model delivering

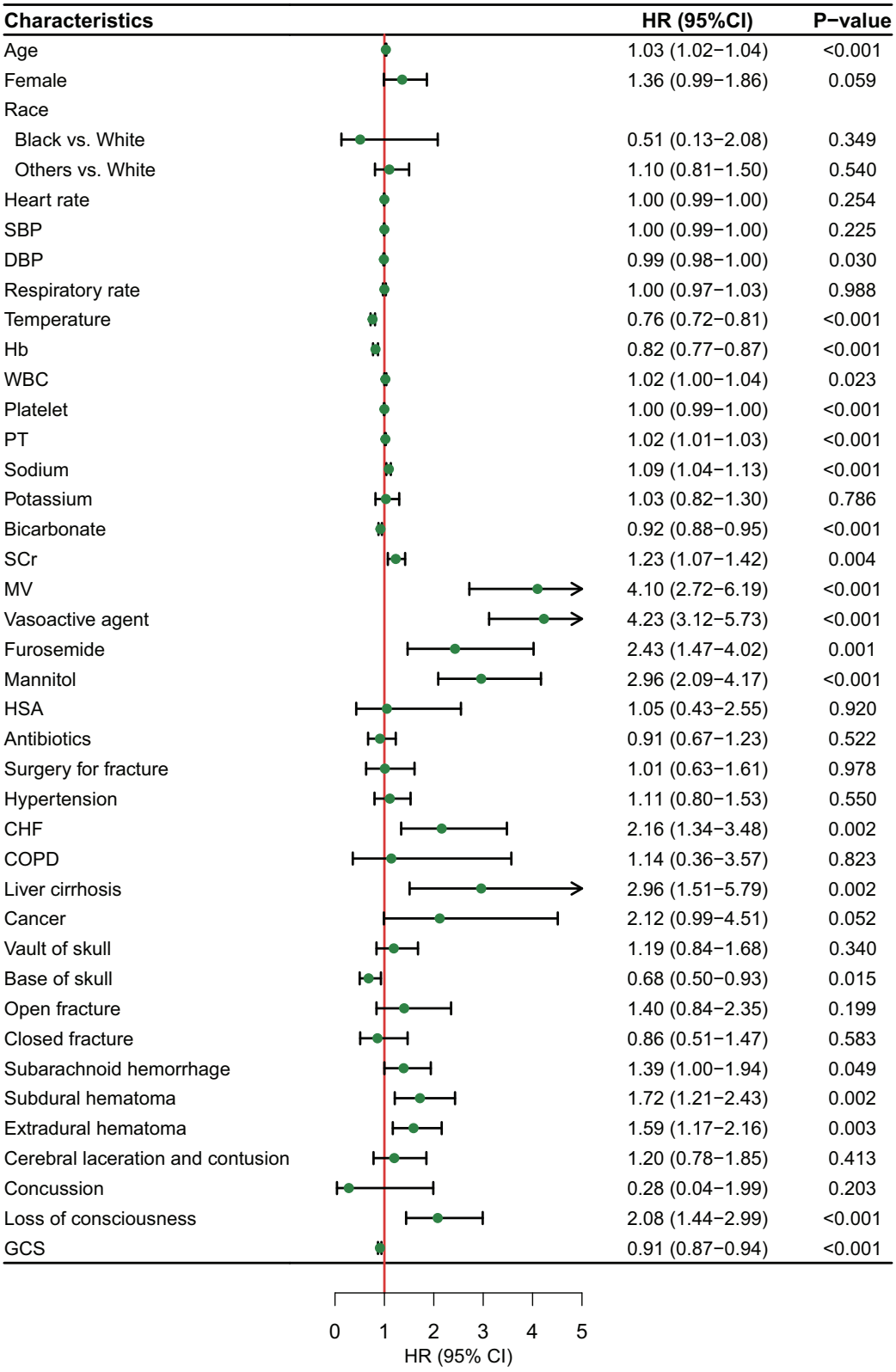

FIGURE 2
Features selection by univariate Cox regression.

the highest specificity at 80.4% (Supplementary Table S4). As a result, the first model with nine factors (age, temperature, sodium, MV, vasoactive agent, mannitol, extradural hematoma, loss of consciousness and GCS score) were included in the nomogram due to its lowest AIC and highest AUC among three models (Figure 6).

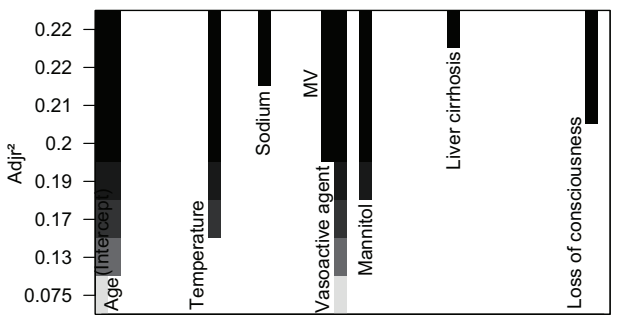

FIGURE 3
Features selection by BSR.

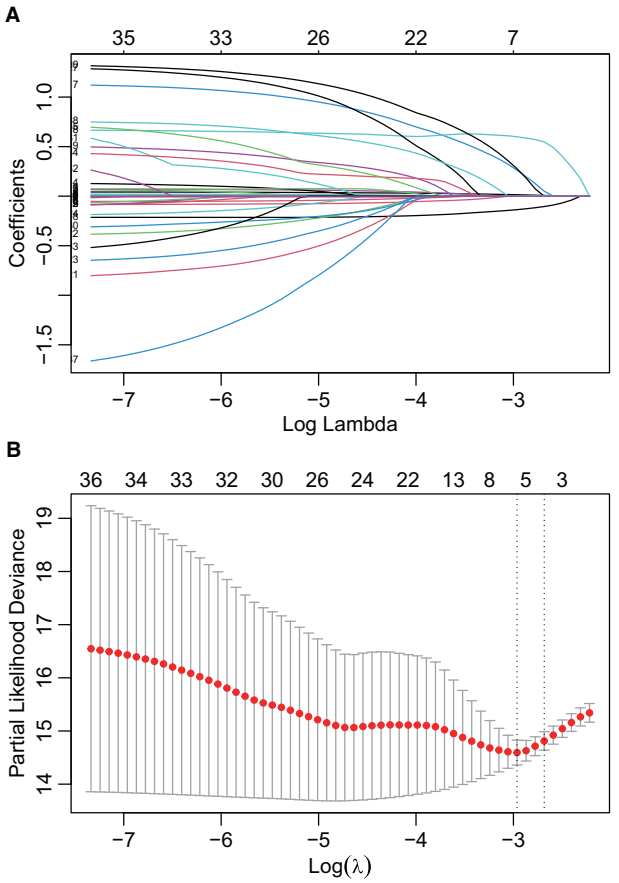

FIGURE 4
Features selection by LASSO. **(A)** LASSO coefficient profiles of the candidate predictors. **(B)** 10-fold cross-validation for tuning parameter selection in the LASSO model.

Evaluation and validation of the nomogram

The VIF values for the mentioned variables were all below 1.5, indicating the absence of collinearity in our model. Our nomogram demonstrated better accuracy than APSIII for predicting the mortality at 28 days in the training set [0.857 (95% CI: 0.827–0.86) vs. 0.761 (95% CI: 0.721–0.802), DeLong's test: $P < 0.001$]. However, in the external validation set, no statistical significance existed [0.853 (95% CI: 0.805–0.900) vs. 0.832 (95% CI: 0.779–0.885), DeLong's test: $P = 0.521$] (Figures 7A, B). The C-index for the training set was 0.832 (95% CI: 0.765–0.883), and for the external validation set, it was 0.829 (95% CI: 0.712–0.905). After 10-fold cross internal validation, this model yielded an AUC value of 0.847 (95% CI: 0.846–0.848) and a C-index of 0.827 (95% CI: 0.826–0.827). Figures 7C, D displayed the calibration curve for the nomogram and it showed good calibration with a low Brier score of 0.091 (95% CI: 0.079–0.103) in the training set and 0.093 (95% CI: 0.074–0.111) in the external validation set, indicating the nomogram-predicted probability was highly consistent with the actual probability. The DCA curves (Figures 7E, F) revealed that the nomogram provided more net benefit than APSIII.

Risk stratification based on the nomogram

Patients were categorized into low, mid, and high-risk groups based on total points calculated using the nomogram. Those with total points below 166.1 were classified as low-risk, while those with scores between 166.1 and 191.1 were considered as mid-risk. Those exceeding 191.1 points were allocated to the high-risk group (Supplementary Figure S3). Kaplan-Meier survival curves indicated that higher points were associated with lower survival probabilities (log-rank test: $P < 0.001$) (Supplementary Figure S4). The cut-off points for risk stratification demonstrated similar discrimination in the training set and the external validation set.

Discussion

Skull fracture is a complex condition that not only disrupts the continuity of cranial bones but is also closely linked to various brain injuries. Those injuries can lead to symptoms ranging from mild alterations in consciousness to severe unconsciousness and even death. In the most severe cases, diffuse damage and swelling can affect the entire brain (11). In the UK, traumatic brain injury (TBI) stands as a leading cause of mortality and disability in individuals under 40 years old, presenting a significant public health challenge (12). Skull fracture, as a clinical event that is relatively easier to diagnose, provide clinicians with a more direct point for assessment and intervention. In emergency medical contexts, the utilization of our model can assist doctors in optimizing resource allocation and enhancing patient management efficiency. The prediction of fatal skull fractures is a field that has not been extensively researched, and our study contributes additional insights to the comprehension and management of skull fractures. In this retrospective study, we evaluated the records of 1,527 adult patients diagnosed with skull fracture from two databases. Nine predictive factors (age, temperature, sodium, MV, vasoactive agent, mannitol, extradural hematoma, loss of consciousness and GCS score) were selected to craft this nomogram. Our findings indicated that age, body temperature, and serum sodium levels were the top three features, carrying the most substantial weight.

Age plays a crucial role in determining the prognosis of various diseases (13–15). After adjusting for multiple factors in our analysis, older age was found to be an independent prognostic factor,

TABLE 2 Final results of backward stepwise multivariate Cox analysis in three models.

Variables	Uni-Cox		BSR		LASSO	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.04 (1.03–1.05)	<0.001	1.04 (1.03–1.05)	<0.001	1.04 (1.03–1.04)	<0.001
Temperature	0.80 (0.74–0.86)	<0.001	0.79 (0.73–0.84)	<0.001	0.83 (0.78–0.89)	<0.001
Hemoglobin	0.91 (0.85–0.99)	0.026				
PT	1.02 (1.00–1.03)	0.027				
Sodium	1.07 (1.03–1.11)	<0.001	1.07 (1.03–1.11)	<0.001		
Bicarbonate	0.95 (0.91–0.99)	0.012				
MV	2.86 (1.80–4.57)	<0.001	2.85 (1.80–4.51)	<0.001	3.57 (2.28–5.58)	<0.001
Vasoactive agent	1.77 (1.25–2.49)	0.001	2.10 (1.50–2.94)	<0.001	2.27 (1.63–3.17)	<0.001
Furosemide	1.67 (0.97–2.88)	0.065				
Mannitol	3.19 (2.19–4.66)	<0.001	3.01 (2.07–4.36)	<0.001		
Liver cirrhosis	2.50 (1.24–5.04)	0.010	3.05 (1.53–6.06)	0.002		
Base of skull	0.74 (0.54–1.02)	0.066				
Extradural hematoma	1.82 (1.32–2.52)	<0.001				
Loss of consciousness	2.29 (1.56–3.38)	<0.001	2.16 (1.48–3.14)	<0.001		

Uni-Cox, univariate Cox regression; BSR, best subset regression; LASSO, least absolute shrinkage and selection operator; HR, hazard ratio; CI, confidence interval; PT, prothrombin time; MV, mechanical ventilation.

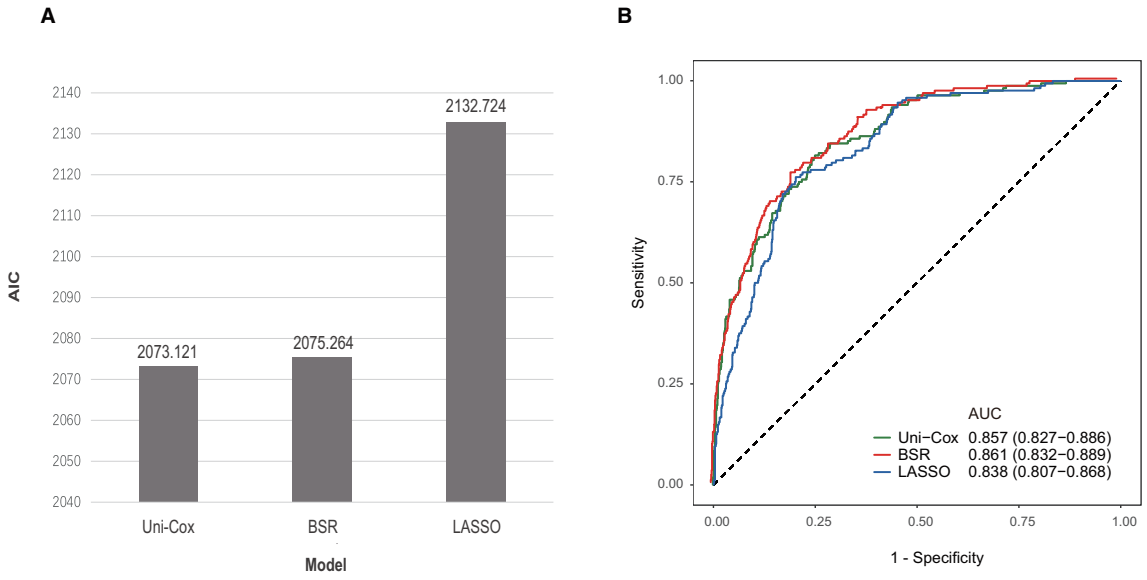

FIGURE 5
Comparison among three models. **(A)** Comparison of AIC values among three models. **(B)** Comparison of AUC values among three models.

exerting a relatively strong influence in the present nomogram. Growing evidence suggests that aging is associated with a decline in the body's immune function, known as "immunosenescence" (16). This weakened immune function can lead to a diminished capacity to defend against infections, which is a significant contributor to mortality in brain trauma patients (17, 18). Additionally, aging increase the vulnerability of microvessels, raising the risk of intracranial hemorrhage after skull fracture (19). Progressive brain atrophy, a characteristic of aging, leads to decreased brain tissue elasticity, increasing the risk of injuries such as diffuse axonal injury, acute subdural hematoma, and others after brain trauma (20, 21). Elderly patients also tend to have more comorbidities, further worsening their prognosis (22). For older patients, it is crucial to be vigilant about their heightened risk of mortality. Early detection and intervention in age-related health issues are key in improving outcomes for these patients.

There is inconsistency in the existing research findings regarding the impact of temperature on the prognosis of TBI

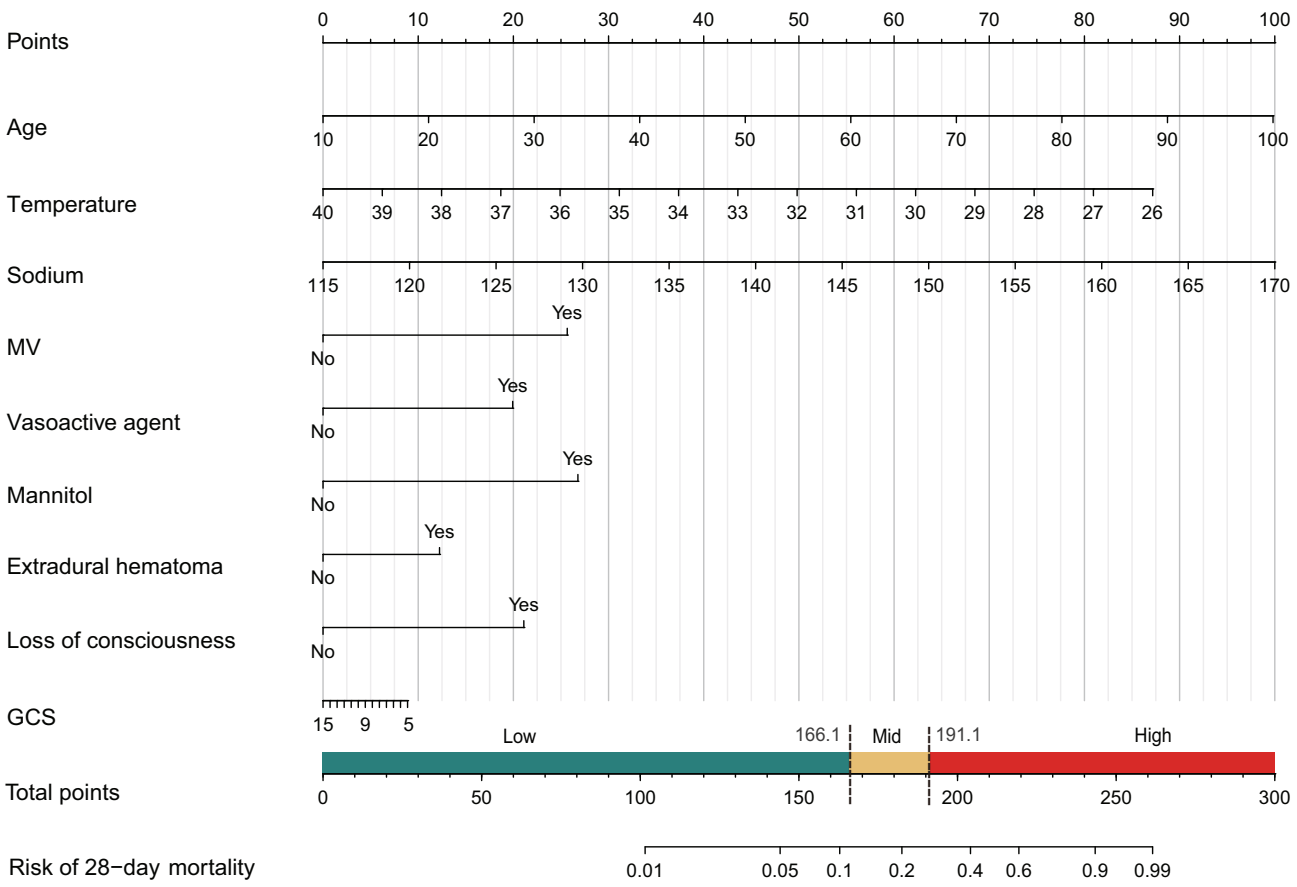

FIGURE 6
Nomogram for predicting the risk of 28-day mortality in patients with skull fracture.

patients. Some theories posit that hyperthermia, by increasing vascular permeability and promoting edema and inflammation, can lead to secondary brain injury in TBI cases. Conversely, lower temperature may slow down post-injury oxidative stress, cellular apoptosis, and inflammatory responses, providing neuroprotective effects for TBI patients (23). However, results from a phase III randomized trial showed no significant improvement in the prognosis of severe pediatric TBI with clinically induced hypothermia (24). Our nomogram highlights that body temperature carries significant weight, and as it decreased, the patient's prognosis worsens. There were several reasons that may be responsible for our findings. One possible explanation was that when body temperature drops, it can cause vasoconstriction and bradycardia, affecting the perfusion and oxygen delivery to vital organs (25). Another reason was perhaps that hypothermia can result in coagulation abnormalities, heightening the risk of bleeding (26). Therefore, we recommend that patients with skull fracture should be closely monitored for body temperature, and further exploration on this issue for such patients is deemed necessary.

Nearly 27% of critically ill patients suffer from various extents of hypernatremia during their hospitalization in the ICU (27). Our findings indicated that increased serum sodium levels were associated with a higher risk of death in patients with skull fractures. Hypernatremia has been proven in medical research to be closely related to poor prognosis. In a study involving COVID-19 patients, patients with hypernatremia had a 2.34–3.05 times higher risk of death compared to those with normal sodium levels (28). Additionally, in a study of cancer patients, patients with hypernatremia had significantly shorter survival times compared to those with normal sodium levels, and their hospital stays were also significantly longer (29). This electrolyte disorder not only reflects an impairment of the body's water balance but can also lead to serious neurological symptoms in patients. Causes of hypernatremia in patients with neurological disorders include the use of hyperosmotic fluids, limited access to free water, or conditions such as diabetes insipidus (30). Hu et al. found that hypernatremia was an independent prognostic factor for critically neurological patients (odds ratio: 1.192, 95% CI: 1.135–1.252, $P < 0.001$) (31). Cho et al. (32) found that hypernatremia had a strong independent association with poor long-term neurological outcomes in survivors of cardiac arrest.

Intracranial hemorrhage plays a pivotal role in evaluating the severity of head trauma. Research indicates that skull fracture is an independent risk factor for intracranial hemorrhage, which can negatively impact the neurological prognosis of patients with TBI (33). Extradural hemorrhage is the most common subtype of hemorrhage occurring in underage patients after skull fractures (34, 35). Skull fracture can tear blood vessels near the skull, leading

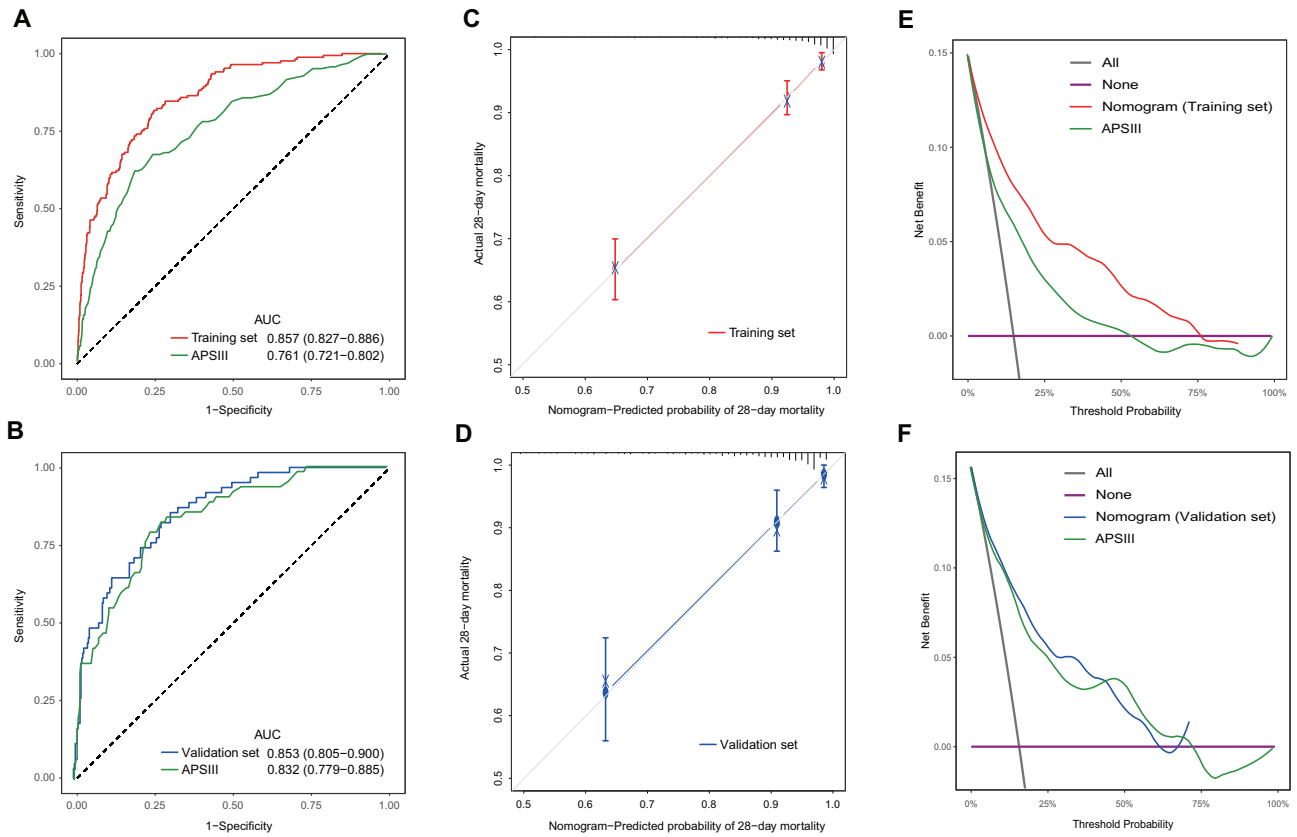

FIGURE 7
Discrimination, calibration, and clinical usefulness of the nomogram in the training and validation sets. **(A)** ROC curves of the nomogram and APSIII in the training set. **(B)** ROC curves of the nomogram and APSIII in the external validation set. **(C)** Calibration curve of the nomogram in the training set. **(D)** Calibration curve of the nomogram in the external validation set. **(E)** Decision curve analysis of the nomogram and APSIII in the training set. **(F)** Decision curve analysis of the nomogram and APSIII in the external validation set.

to extradural hematoma (36). Our results indicated that extradural hematoma significantly influences the prognosis of skull fracture patients, causing brain tissue compression, increased intracranial pressure, and the risk of neural structure injury (37). This finding highlights the critical need for immediate identification of extradural hematoma in these patients. Understanding the grave implications of extradural hematoma in skull fractures enables clinicians to allocate resources more effectively and improve patient outcomes through targeted interventions.

In the management of brain injury patients, preventing hypoxia and hypotension is paramount. Mechanical ventilation and vasoactive agents are often used for this purpose. Our nomogram revealed that mechanical ventilation and vasoactive agents use were associated with higher mortality. In the ICU, patients who require mechanical ventilation and vasoactive drugs from the first day tend to have more severe conditions compared to those who do not need these interventions. The most common site of infection in patients with TBI admitted to ICU is respiratory system (38). Mechanical ventilation is considered a risk factor for ventilator-associated pneumonia, and the risk for TBI patients is approximately 42% (39). In order to achieve blood pressure and cerebral perfusion pressure (CPP) targets, we administer vasoactive drugs, such as norepinephrine (a widely used vasopressor in the worldwide). However, there is evidence pointing to its potential to induce vasospasm after intracranial hemorrhage, leading to a decrease in cerebral oxygenation (40). It's important to note that the association between vasoactive drugs use and increased mortality does not imply that these drugs are fatal. They are essential in specific circumstances, but their use should be carefully considered and monitored to ensure the best treatment outcomes and patient safety. Further research is needed to explore the relationship and potential mechanisms between vasoactive drugs and the prognosis of patients with skull fracture.

Increased intracranial pressure (ICP) is strongly linked to poor neurological outcomes and mortality in acute TBI patients (41). In clinical practice, mannitol is routinely employed to address elevated intracranial pressure. Nonetheless, in certain studies related to TBI, the early use of mannitol was found to be independently associated with a higher occurrence of AKI (42). Mannitol's diuretic action may lead to hypovolemia and hypoperfusion, posing a significant risk for increased morbidity and mortality in patients with brain pathology (43). Our analysis showed that mannitol use was associated with poor patient outcomes. Further studies are needed to investigate the mechanisms behind this association and explore other factors that may influence the correlation between mannitol usage and mortality risk. Finally, our analysis also revealed that the loss of consciousness contributed to an augmented risk of 28-day mortality. The occurrence of consciousness loss in these

patients may indicate more severe brain damage and consequent neurological dysfunction. This severe neurological dysfunction may subject them to a greater incidence of complications and risks during their hospitalization, ultimately raising the probability of death.

In this study, by employing univariate Cox regression, BSR, LASSO, and backward stepwise multivariable Cox regression, our analysis effectively reduced the risk of overfitting and underfitting. Moreover, the availability of all variables in the final model guarantees the practicality and clinical utility of this nomogram. However, there are limitations to consider. Not all patients' diagnostic information in the public databases was consistently well-defined, impacting the precision of our results, particularly in cases with ambiguous diagnoses like "unspecified" fracture types. Additionally, the limited data in the databases result in the exclusion of critical factors that could impact patients' survival, such as detailed information on injury causes and processes, which could have informed fracture site analysis and severity assessment. For issues with inconsistent diagnostic information, we can build separate models for patients with different diagnoses in the future. For ambiguous diagnosis issues, we can try to exclude these patients during data preprocessing. For the challenge of limited data, developing models based on large datasets from multiple centers is a viable approach. We believe that implementing these measures will enhance the stability and generalizability of our model.

Conclusion

In summary, we have successfully developed and validated the first prognostic model that integrates nine clinical features to effectively predict the 28-day mortality risk in ICU patients with skull fractures. Early intervention in modifiable variables in the model, such as body temperature and serum sodium, can significantly improve the prognosis in skull fracture patients. Previous studies relating to skull fracture emphasized risk factors but didn't combine them into a full model. Our research addressed this gap by developing a comprehensive model that integrates several variables, potentially aiding clinicians in making well-informed decisions regarding the management of skull fractures.

Data availability statement

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

Author contributions

JT: Writing—original draft. ZZ: Writing—review & editing. MN: Writing—review & editing. CW: Writing—review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We extend our sincere gratitude to the esteemed team at the Laboratory for Computational Physiology, Massachusetts Institute of Technology, for their unwavering dedication in maintaining the accessibility of the MIMIC and eICU-CRD databases.

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.2023.1338545/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 18 March 2024
DOI 10.3389/fneur.2024.1349710

OPEN ACCESS

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RECEIVED 05 December 2023
ACCEPTED 08 March 2024
PUBLISHED 18 March 2024

CITATION
Wang X, Li X, Sun J, Wang M, Lang W and Xu X (2024) Relationship between sodium level and in-hospital mortality in traumatic brain injury patients of MIMIC IV database. *Front. Neurol.* 15:1349710.
doi: 10.3389/fneur.2024.1349710

Relationship between sodium level and in-hospital mortality in traumatic brain injury patients of MIMIC IV database

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Background: An association between prognosis and high sodium levels in Traumatic Brain Injury (TBI) patients in Intensive Care Units (ICUs) has been noted, but limited research exists on the ideal sodium level in these patients or the impact on early mortality, using the MIMIC-IV database.

Methods: A retrospective survey was conducted on TBI patients from the MIMIC-IV database. Patients were divided into two categories based on their highest serum sodium level within 24 h of admission exceeding 145 mmol/L: those with hypernatremia, and those with moderate-to-low sodium levels. Collected covariates encompasses demographic, clinical, laboratory, and intervention variables. A multivariate logistic regression model was implemented to forecast in-hospital mortality.

Results: The study included 1749 TBI patients, with 209 (11.5%) experiencing in-hospital deaths. A non-linear test exposed an L-shaped correlation between sodium level and in-hospital mortality, with mortality rates increasing after a turning point at 144.1 mmol/L. Compared to the moderate-to-low group's 9.3% mortality rate, the hypernatremia group had a significantly higher mortality rate of 25.3% (crude odds ratio = 3.32, 95% confidence interval: 2.37 ~ 4.64, $p < 0.001$). After adjusting for all covariates, the hypernatremia group continued to show a significant correlation with higher mortality risk (adjusted odds ratio = 2.19, 95% confidence interval: 1.38 ~ 3.47, $p = 0.001$). This trend remained consistent regardless of the analyses stratification.

Conclusion: The study reveals an L-shaped relationship between sodium levels and in-hospital deaths, with a pivotal point at 144.1 mmol/L. TBI patients displaying hypernatremia were independently linked to higher in-hospital mortality, underlining the need for further studies into targeted management of sodium levels in these patients.

KEYWORDS

traumatic brain injury, hypernatremia, mortality, MIMIC IV database, ICU

Introduction

Traumatic brain injury (TBI) affect nearly 69 million people per year, often resulting in long-lasting disability and mortality (1). Despite the pervasiveness of this issue, effective treatments for TBI are limited. Hypernatremia is commonly identified in TBI patients admitted to Intensive Care Units (ICUs) (2). The mechanisms contributing to hypernatremia in these patients are complex, encompassing central diabetes insipidus, osmotic agent administration, high sodium infusion and imbalance of fluid intake and output (3). Several studies suggest an independent correlation between hypernatremia and mortality following severe TBI (3, 4). The causal relationship, however, remains indistinct as hypernatremia can indicate both disease severity and a therapeutic target for fundamental medication such as mannitol and/or hypertonic saline (5). Additional research is imperative to understand the prognostic implication of sodium levels in TBI patients and to clarify the optimal sodium level for these patients during ICU admission although the causal relationship cannot be established. The aim of the current study is to evaluate the impact of sodium levels on in-hospital mortality among patients with severe TBI.

Method

Study population

This retrospective study exploits patient data from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) cohort, a single-center, longitudinal cohort from 2008 to 2019. The MIMIC-IV database comprises diverse patient information from ICUs. We completed a training programme facilitated by the PhysioNet team and secured official approval to use the MIMIC-IV database from the review boards of the "Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center" (ID: 11744558). Because the patient data utilized in this study was anonymized within the database, informed consent was unnecessary. The data extraction code, available on GitHub[1] (6), was employed, and the study was conducted in adherence to the STROBE ("Strengthening the Reporting of Observational Studies in Epidemiology") guidelines (7).

Inclusion and exclusion criteria

TBI patient data extracted from the database using the diagnostic codes of ICD-9 or ICD-10 (International Classification of Disease, Ninth and Tenth Versions; ICD-9: 85*; ICD-10: S06*) were included in this study. The criteria defined for inclusion were: (1) patients aged 18 years or older; (2) patients with an ICU length of stay (LOS) lasting 24 h or more; and (3) consideration only of the initial ICU stay record. Meanwhile, the exclusion criteria consisted of: (1) patients younger than 18 years and (2) patients with an ICU stay less than 24 h.

1 http://github.com/MIT-LCP/mimic-iv

Data extraction

Structured Query Language (SQL) was employed for data extraction. Variables, collected within 24 h of ICU admission, were extracted. If repeated test results presented themselves, only the worst was selected. These variables include:

1. Basic patient characteristics such as sex, admission age, race, admission time, ICD code, and in-hospital death.
2. Vital signs like temperature, mean blood pressure (MBP), heart rate, and SpO2.
3. Illness severity scores, which included the SOFA score, SAPS II, GCS, and Charlson comorbidity index.
4. Laboratory results such as WBC count, creatinine levels, HCT, etc.
5. Treatment methods, such as mechanical ventilation, hypersaline infusion.
6. Comorbidities—myocardial infarction, peripheral vascular disease, dementia, COPD, malignant cancer, renal disease, and severe liver disease, among others.

Variable definition and outcomes

The Hypernatremia group was characterized by a sodium level exceeding 145 mmoL/L during the first 24 h after ICU admission, while the moderate to low group had a sodium level of 145 mmoL/L or below. The primary objective of this study was to explore in-hospital mortality as the chief outcome.

Statistical analysis

Patient baseline characteristics were stratified by differing sodium level groups. Continuous data were represented as either mean ± standard deviation or median (inter-quartile range), while categorical variables were depicted as numbers (percentages) where suitable. Statistical comparisons between the two groups employed the chi-square test or Fisher's exact test for categorical variables, and continuous variables were assessed via the analysis of variance test or rank-sum test. No imputation methods were used for missing data. Patients with missing data (with a missing rate below 1%) on variables like mean glucose level, WBC, BUN, and GCS were excluded. If a patient was intubated and could not provide a verbal score for the Glasgow Coma Scale (GCS), it was estimated from the eye and motor scores, as reported in previous studies (8).

Univariable logistic regression was utilized to assess the potential effect of sodium levels on in-hospital-death and to screen for confounders. To further analyze the relationship between Hypernatremia and in-hospital death, a multivariable logistic regression model was adopted, with models adjusted by potential confounders.

A restricted cubic spline was applied to investigate potential nonlinear relationships between sodium level and in-hospital mortality, adjusting the analysis for factors including age, gender, MBP, heart rate, spo2, glucose, platelets, hematocrit, hemoglobin, WBC, potassium, BUN, creatinine, Charlson comorbidity index, SAPSII, GCS, and length of stay (LOS) in ICU. Inflection point analysis was undertaken to identify the optimal serum sodium level

corresponding to the lowest mortality. A likelihood ratio test was conducted to gauge how closely in-hospital death and sodium levels were related. Heterogeneity across subgroups was examined through logistic proportional hazards analysis, and a likelihood ratio test evaluated the interactions.

A two-tailed test with a threshold of $p < 0.05$ determined statistical significance. The data were analyzed using the R software package (R version 4.0.3) and Free Statistics software version 1.7.

Result

Baseline characteristics

We identified 2,422 individuals diagnosed with Traumatic Brain Injury (TBI) who were first admitted to the ICU. Out of these, 421 patients had an ICU stay shorter than one day. With missing data cases excluded, 1,749 records remained for our final cohort analysis. The process of participant admission and exclusion is depicted in Figure 1.

Table 1 outlines the clinical characteristics of the selected participants. The cohort comprised of 1,749 patients, with an average age of 65.9 ± 20.3 years. The majority were males (62.1%; $n = 1{,}087$). A total of 202 patients (11.5%) did not survive their hospital stay. We classified 249 patients with higher sodium levels into a hypernatremia group. This group showed younger patient age and lesser prevalence of comorbidities such as malignant cancer but higher White Blood Cell (WBC) count and potassium levels. The Simplified Acute Physiology Score II (SAPSII) was higher and Glasgow Coma Scale (GCS) lower in the hypernatremia group, which also contained most of the mechanically ventilated patients. More frequently administered with hypertonic saline, the hypernatremia group had a longer ICU-Length Of Stay (LOS) and a higher mortality rate compared to the moderate-to-low group (25.3% vs. 9.3%). Refer to Table 1 for details.

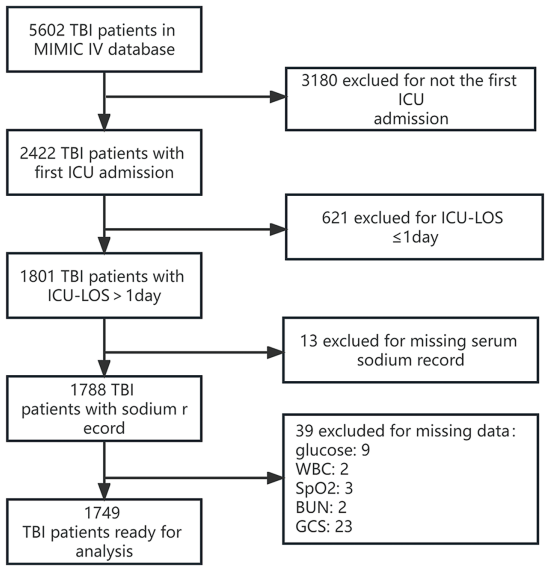

FIGURE 1
Detailed flowchart illustrating the participant recruitment process. GCS, Glasgow Coma Scale; WBC, white blood cell count; ICU, intensive care unit.

Relationship between sodium level on in-hospital mortality

Our univariate logistic regression analysis (Table 2) indicates an increasing in-hospital mortality in line with rising sodium levels. Specifically, each unit (mmol/L) increase in sodium level corresponded to a 10% rise in the odds of in-hospital death (OR:1.1; 95%CI:1.071.14; $p < 0.001$). The hypernatremia group exhibited a 3.32 times higher mortality rate relative to the reference group (crude odds ratio = 3.32, 95% confidence interval: 2.374.64, $p < 0.001$).

After accounting for confounding factors in the multivariate logistic models (Table 3), patients in the hypernatremia group were found to have 2.17 times the risk of in-hospital mortality compared to the reference group (adjusted odds ratio = 2.17, 95% confidence interval: 1.36 ~ 3.46, $p = 0.001$).

Further investigation into the relationship between sodium levels and in-hospital mortality was conducted through multivariable-adjusted restricted cubic spline analyses. There emerged a J-shaped association, indicative of a non-linear relationship between sodium levels and mortality (Figure 2). The inflection point for sodium levels was about 144.1 mmol/L (95% confidence interval: 143.505 ~ 144.785, $p = 0.05$) (Table 4). Beyond this threshold, every additional 1 mmol/L of sodium level led to a 9.7% rise in in-hospital mortality odds (OR = 1.097; 95%CI:1.002 ~ 1.202, $p = 0.05$). Below this point, sodium level increases did not impact in-hospital mortality rates (OR = 0.992 (0.936 ~ 1.051), $p = 0.7856$).

Sensitivity analysis

Through multivariable logistic models, we carefully adjusted for diverse confounding factors to gauge the relationship between sodium levels and in-hospital mortality. Intriguingly, this association remained consistent across all models (refer to Table 3). To validate the resilience of our results, subgroup analyses were performed based on a variety of confounding variables such as age, gender, GCS, and comorbidities like COPD, congestive heart failure, and renal disease (depicted in Figure 3). These analyses reaffirmed our preliminary findings. The potential interaction within the COPD subgroup could be attributed to its relatively small size. No significant interactions were detected in any other sub-groups (all $p > 0.05$) (see Figure 3).

To delve deeper into the relationship between sodium levels and in-hospital mortality, we reclassified our cohort into three categories: the hyponatremia group ($n = 117$), which includes patients with sodium levels below 135 mmol/L; the hypernatremia group ($n = 249$), comprising patients with sodium levels above 145 mmol/L; and the normonatremia group ($n = 1{,}383$), consisting of patients with sodium levels ranging from 135 to 145 mmol/L. We employed both univariate and multivariate logistic regression analyses to examine this association, as presented in Table 5. Compared to the normonatremia group, the hyponatremia group did not exhibit a significant association with in-hospital mortality (crude OR = 1.02, 95% CI: 0.53–1.94, $p = 0.958$; adjusted OR = 0.75, 95% CI: 0.34–1.63, $p = 0.466$). In contrast, the hypernatremia group demonstrated a significant association with increased in-hospital mortality (crude OR = 3.32, 95% CI: 2.37–4.66, $p < 0.001$; adjusted OR = 2.11, 95% CI: 1.32–3.38, $p = 0.002$).

TABLE 1 Characteristic of patients categorized by sodium level.

	Total (n = 1749)	Moderate to low group (n = 1,500)	Hypernatremia group (n = 249)	p
Demographics				
Age, Mean (SD), year	65.9 (20.3)	66.8 (20.0)	60.7 (21.3)	**<0.001**
Sex, n (%)				0.647
Male	1,087 (62.1)	929 (61.9)	158 (63.5)	
Female	662 (37.9)	571 (38.1)	91 (36.5)	
Vital signs, Mean (SD)				
MBP, mmHg	81.9 (10.1)	81.8 (10.1)	82.6 (10.1)	0.227
temperature, °C	37.0 (0.5)	37.0 (0.5)	37.1 (0.7)	**0.006**
SpO2, %	97.4 (1.7)	97.4 (1.7)	97.8 (1.8)	**<0.001**
Lab test, Mean (SD)				
Glucose, mg/dl	132.8 (40.8)	132.5 (40.6)	134.8 (42.2)	0.396
Hematocrit, %	36.8 (5.7)	36.8 (5.6)	37.3 (5.9)	0.2
Hemoglobin, g/dL	12.3 (2.0)	12.3 (2.0)	12.3 (2.1)	0.948
Platelets, 10^9/L	221.8 (97.3)	223.4 (98.3)	212.1 (91.1)	0.092
WBC, 10^9/L	12.9 (7.4)	12.7 (7.5)	14.1 (7.0)	**0.004**
BUN, mg/dl	20.8 (14.1)	20.7 (14.2)	21.4 (13.3)	0.451
Creatinine, mg/dl	1.2 (1.0)	1.2 (1.0)	1.2 (0.8)	0.331
Potassium, mmol/L	4.4 (0.8)	4.4 (0.8)	4.5 (0.8)	0.023
Sodium, mmol/L	140.6 (4.8)	139.4 (3.5)	147.7 (4.9)	**<0.001**
Severity score, Mean (SD)				
charlson_comorbidity_index	4.3 (2.8)	4.4 (2.8)	3.9 (2.9)	**0.004**
SAPSII	33.4 (11.8)	32.8 (11.6)	36.9 (12.5)	**<0.001**
GCS	11.1 (3.6)	11.4 (3.4)	9.4 (4.2)	**<0.001**
Commodities, n (%)				
myocardial_infarct	140 (8.0)	122 (8.1)	18 (7.2)	0.626
congestive_heart_failure	232 (13.3)	198 (13.2)	34 (13.7)	0.845
Diabetes	300 (17.2)	267 (17.8)	33 (13.3)	0.078
renal_disease	214 (12.2)	185 (12.3)	29 (11.6)	0.759
malignant_cancer	74 (4.2)	70 (4.7)	4 (1.6)	**0.026**
Interventions, n (%)				
Ventilation	711 (40.7)	556 (37.1)	155 (62.2)	**<0.001**
Hypertonic saline	112 (6.4)	74 (4.9)	38 (15.3)	**<0.001**
Brain surgery	398 (22.8)	343 (22.9)	55 (22.1)	0.786
Outcomes				
In-hospital death, n (%)	202 (11.5)	139 (9.3)	63 (25.3)	**<0.001**
LOS-ICU, Mean(SD)	4.9 (6.0)	4.5 (5.2)	7.1 (9.3)	**<0.001**

SAPS, simplified acute physiology score; COPD, chronic obstructive pulmonary disease; MBP, mean blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen. GCS, Glasgow coma scale; LOS-ICU, length of stay in intensive care unit; SD, standard derivation; SASPII, Simplified Acute Physiology Score II. Bold values indicate statistical significance ($p < 0.05$).

Discussion

In this investigation of adult Traumatic Brain Injury (TBI) patients from MIMIC-IV, we observed a higher in-hospital mortality rate for those patients with hypernatremia. Restricted Cubic Splines (RCS) analysis revealed an L-shaped dose–response correlation between serum sodium concentration and mortality risk. We determined the ideal serum sodium concentration for TBI patients to be ≤144.1 mmol/L. Our study reveals that hypernatremia independently correlates with mortality during hospitalization and that a serum sodium level of ≤144.1 mmol/L might be an effective target for TBI treatment management. To the best of our understanding, this report distinguishes itself as a pioneering effort in establishing a patient-specific threshold for serum sodium levels, exclusive to Traumatic Brain Injury (TBI) patients admitted to the Intensive Care Unit (ICU).

TABLE 2 Univariate logistic regression evaluating the association between baseline characteristics and in-hospital mortality.

Variable	OR_95CI	*p*_value
Sodium level	1.1 (1.07 ~ 1.14)	**<0.001**
Hypernatremia group	3.32 (2.37 ~ 4.64)	**<0.001**
Sex	1.19 (0.89 ~ 1.61)	0.245
Age	1.02 (1.01 ~ 1.03)	**<0.001**
GCS	0.67 (0.63 ~ 0.7)	**<0.001**
Heart_rate	1.02 (1.01 ~ 1.03)	**<0.001**
MBP	0.97 (0.96 ~ 0.99)	**<0.001**
SpO2	1.31 (1.19 ~ 1.45)	**<0.001**
Glucose	1.01 (1 ~ 1.01)	**<0.001**
Hematocrit	0.95 (0.92 ~ 0.97)	**<0.001**
Hemoglobin	0.85 (0.79 ~ 0.92)	**<0.001**
Platelets	1 (1 ~ 1)	0.236
WBC	1.03 (1.01 ~ 1.05)	**0.001**
BUN	1.03 (1.02 ~ 1.03)	**<0.001**
Bicarbonate	0.94 (0.9 ~ 0.98)	**0.006**
Creatinine	1.19 (1.06 ~ 1.32)	**0.002**
Charlson comorbidity index	1.14 (1.08 ~ 1.2)	**<0.001**
SAPSII	1.08 (1.07 ~ 1.1)	**<0.001**
Ventilation	6.06 (4.29 ~ 8.56)	**<0.001**
Brain surgery	1 (0.71 ~ 1.42)	0.995
Hypertonic saline	2.96 (1.88 ~ 4.64)	**<0.001**

SAPS, simplified acute physiology score; COPD, chronic obstructive pulmonary disease; MBP, mean blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen. GCS, Glasgow coma scale; SASPII, Simplified Acute Physiology Score II. Bold values indicate statistical significance ($p < 0.05$).

TABLE 3 Multivariable logistic regression models evaluating the association between hypernatremia and in-hospital mortality.

Model	crude. OR_95CI	crude.*p*_value	adj. OR_95CI	adj.*p*_value
Model 1	3.32 (2.37 ~ 4.64)	<0.001	3.85 (2.72 ~ 5.44)	<0.001
Model 2			2.33 (1.5 ~ 3.6)	<0.001
Model 3			2.28 (1.44 ~ 3.6)	<0.001
Model 4			2.17 (1.36 ~ 3.46)	0.001

Model 1: Adjusted for sex and age.
Model 2: Adjusted for Model 1 + GCS, Charlson comorbidity index and SASPII.
Model 3: Adjusted for Model2 + heart rate + MBP+ SpO2+ hematocrit + hemoglobin + platelets + WBC+ BUN+ bicarbonate + Creatinine + glucose.
Model 4:Adjuste for Model3+ ventilation, hypertonic saline and brain surgery.
OR, odd ratio; CI, confident interval.

Hypernatremia, often induced by water loss due to ventilation, sedation therapy, or osmotic diuretic administration, frequently occurs in TBI patients (9). The use of hypertonic saline and mannitol to manage intracranial pressure commonly exacerbates hypernatremia especially when it becomes a treatment target for elevated ICP (5, 10). Additionally, hyperosmolar therapy-related acute kidney injury can intensify hypernatremia (3). It can also result from hypothalamic or pituitary gland dysfunction post-TBI, known as central diabetes insipidus, potentially indicating disease severity (5).

Maggiore et al. corroborated the association between the prevalence of hypernatremia and increased mortality rates in individuals suffering from severe traumatic brain injury. They identified that the emergence of hypernatremia was, in part, attributable to central diabetes insipidus (4).

We acknowledge that our study has the significant limitation like previous study's that we also cannot establish causal relationship between hypernatremia and outcome. In an expansive healthcare database encompassing data from over 90,000 patients with traumatic brain injury (TBI), there was a clear correlation between hypernatremia and less favorable outcomes in this patient population (11). Previous studies reported hypernatremia and mortality associations in various neurological critical conditions. In neurologic ICUs, severe hypernatremia (serum sodium >160 mmol/L) was independently linked to in-hospital mortality (12). This observation was consistent with findings in pediatric study focusing on severe traumatic brain injury(TBI) (13). Serum sodium concentration has been used to predict ICU deaths in the neurological ICU, with an optimal cut-off at 147.55 mmol/L (14). Takahiro et al. found an L-shaped dose–response association between serum sodium concentration and mortality in cerebrovascular diseases, identifying a 147 mmol/L maximum threshold through restricted cubic splines analysis (15). These findings align with our study, though the slightly higher cut-off value may result from the different population studied. The discrepancy between the results observed by Tan and colleagues and our own can primarily be attributed to differences in patient demographics and injury severity within their study (16). Specifically, patients in their research cohort presented with a more severe average Glasgow Coma Scale (GCS) score (11.1 compared to our cohort's 6) and were of a younger median age (52 versus 34 years, respectively). Recent meta-analyses further bolster the conclusion that hypernatremia is associated with heightened mortality risk (17).

The reason of hypernatremia on higher mortality can be listed as follows: Hypernatraemia is associated with various neuromuscular manifestations, such as muscle weakness, that can prolong the length of ICU stay and duration of mechanical ventilation which may increase mortality (18). Hypernatremia can lead to organ dysfunction, including abnormal hepatic function, disturbance of insulin resistance, cardiac dysfunction and muscle injury (14, 19). Hypernatremia can injure myelin and even cause secondary brain injury by increased cellular dehydration and decreased cerebral edema (3).

Mild hypernatremia induced by hyperosmolar agents that can effectively decrease ICP may result in a favorable prognosis (20, 21). Thus, maintaining sodium levels within an acceptable range is crucial. In our study, we determined the optimal target serum sodium concentration for TBI patients to be ≤144.1 mmol/L, offering a valuable therapeutic outlook for TBI. The lack of a lower sodium level threshold observation could be due to the inclusion of data within 24 h of ICU admission since hyponatremia often occurs days after TBI (22).

This study had several limitations. Primarily, the dataset's nature prevented us from ruling out the specific etiology of hypernatremia, or adjusting properly for baseline factor influences on hypernatremia. This study is constrained by the limitation that in-hospital mortality was the sole outcome variable utilized in our

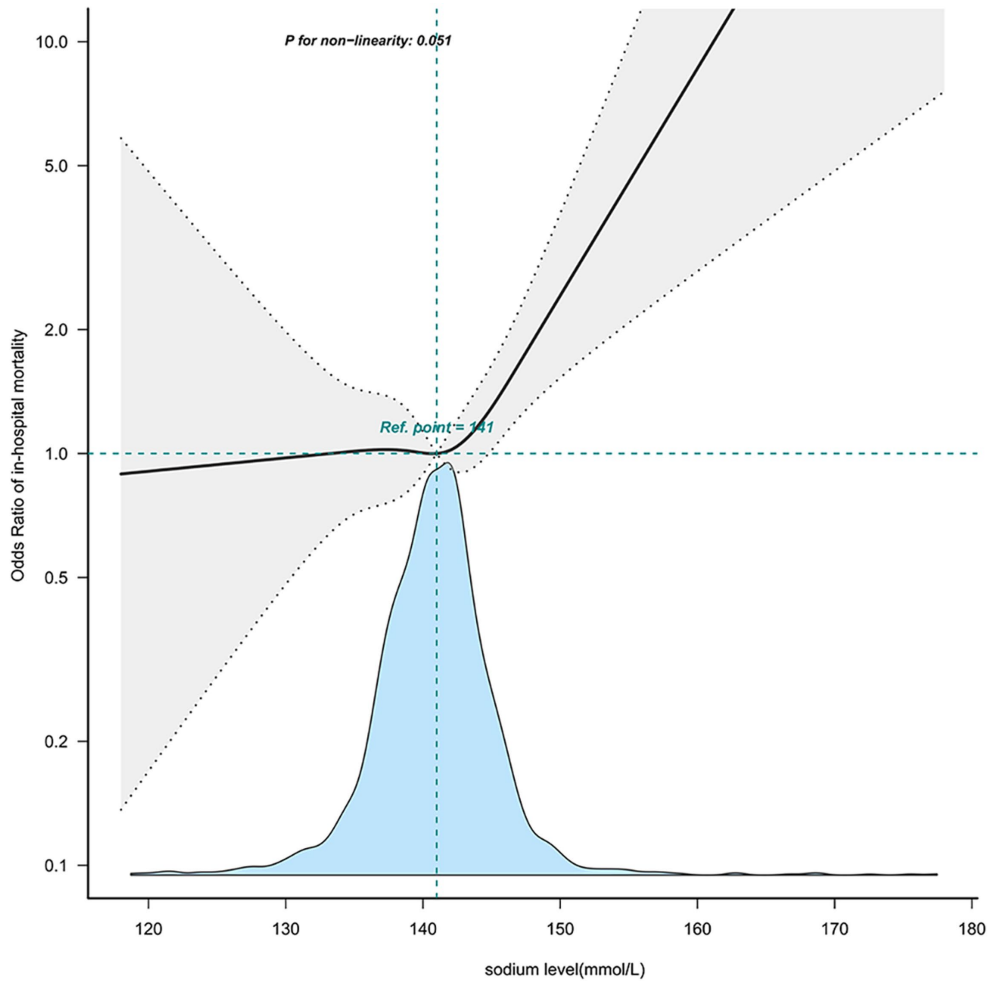

FIGURE 2
The nonlinear relationship between sodium level and in-hospital mortality. This curve illustrates the mortality fluctuation across varying sodium levels within the cohort, using the median level of 141 mmol/L as a reference point. The curve notably demonstrates a significant uptick in mortality commencing within the 141–150 mmol/L sodium range (P for non – linearity = 0.051). Adjusted sex, age, stroke type, GCS, heart_rate, MBP, SpO2, hematocrit, hemoglobin, platelet, WBC, BUN, bicarbonate, creatinine, Charlson_comorbidity_index, SAPSii, glucose, ventilation status. GCS, Glasgow Coma Scale; WBC, white blood cell count; BUN, blood urea nitrogen; MBP, mean blood pressure.

TABLE 4 The nonlinear relationship between sodium level and in-hospital mortality.

Threshold	OR(95% CI)	*p*
Threshold point	144.145 (143.505,144.785)	–
Slope<144.145	0.992 (0.936 ~ 1.051)	0.7856
Slope ≥ 144.145	1.097 (1.002 ~ 1.202)	0.0459
Likelihood ratio test	–	0.05

Adjusted: sex + age + GCS+ heart rate + MBP+ SpO2+ hematocrit + hemoglobin + platelets + WBC+ BUN+ bicarbonate + creatinine + Charlson comorbidity index + glucose + ventilation + SASPII+ brain surgery. OR, odd ratio; CI, confident interval.

analyses. More significant outcome measures, such as the Glasgow Outcome Scale-Extended (GOSE), which provide a more comprehensive evaluation of patient functionality beyond mortality, could not be obtained from the MIMIC-IV database. Another critical limitation of our research is the absence of intracranial pressure (ICP) values, which are a pivotal confounder for analysis. The omission of these values is due to an excessively high percentage of missing data, rendering their use infeasible for our study. Also, being a retrospective study, the test timing was not randomly planned potentially leading to the exclusion of some hypernatremic patients and the failure to use sodium over time to analyze the association to the outcome. Furthermore, MIMIC-IV being a single-center cohort may inherently carry biases related to specific medical practice styles. Therefore, validating our findings across different populations would require prospective studies in multiple ICUs.

Conclusion

The current investigation conclusively establishes hypernatraemia in 24 h as a mortality marker in critically ill TBI patients. Additionally, it designates a specific cut-off point for serum sodium concentration at 144.1 mEq/L, beyond which the mortality risk escalates. These

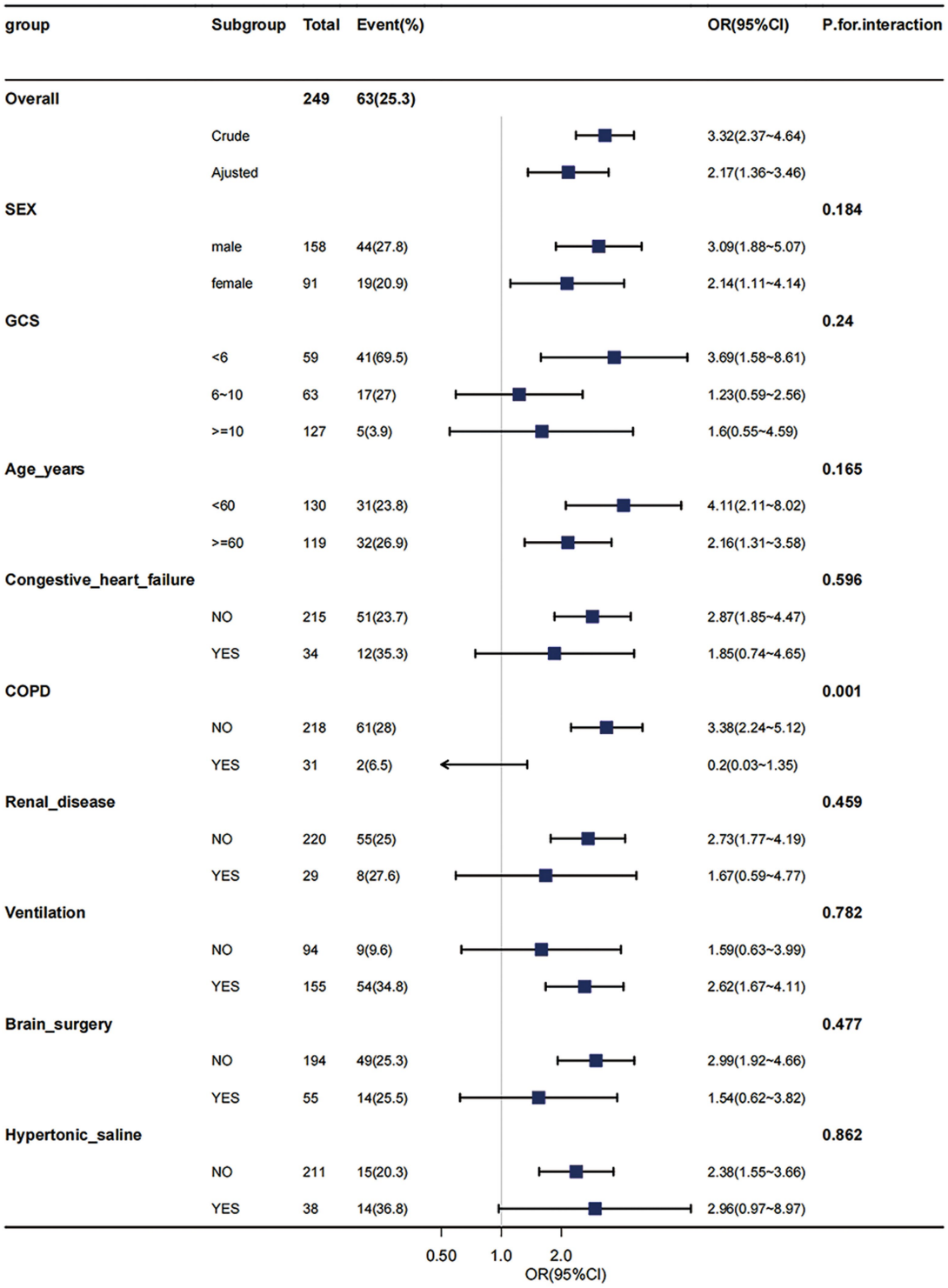

FIGURE 3
Effect size of hypernatremia on in-hospital mortality in different subgroups. Subgroup analyses were executed to assess patients with varied demographics, including age, gender, Glasgow Coma Scale (GCS) scores, and the presence of comorbid conditions such as Chronic Obstructive Pulmonary Disease (COPD), congestive heart failure, and renal disease. These analyses were conducted within the hypernatremia group (comprising 249 patients) and compared with those in the moderate-to-low sodium level group. The results from this subgroup analyses have demonstrated consistent and robust findings. COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale, WBC, white blood cell count; BUN, blood urea nitrogen. Adjusted: MBP, heart rate, SpO2, hematocrit, hemoglobin, platelets, WBC, BUN, bicarbonate, creatinine, Charlson comorbidity index, SAPSii, glucose.

TABLE 5 The association between different sodium levels with in-hospital mortality.

Variable	n.total	n.event_%	crude. OR_95CI	crude.*p*_value	adj.OR_95CI	adj.*p*_value
Normal group	1,383	128 (9.3)	1 (Ref)		1 (Ref)	
Hyponatremia group	117	11 (9.4)	1.02 (0.53 ~ 1.94)	0.958	0.75 (0.34 ~ 1.63)	0.466
Hypernatremia group	249	63 (25.3)	3.32 (2.37 ~ 4.66)	<0.001	2.11 (1.32 ~ 3.38)	0.002

Mutivriable logistic regression used variables adjusted in model 4 showed in Table 3. OR, odd ratio; CI, confident interval.

insights are instrumental for healthcare professionals tending to such critically ill TBI individuals.

Data availability statement

The datasets presented in this article are not readily available because the data utilized in this study were obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV) Clinical Database (23). Requests for access to these datasets should be directed to PhysioNet (24, 25). Requests to access the datasets should be directed to www.physionet.org/.

Ethics statement

The studies involving humans were approved by review boards of the "Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center." 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 Written consent from participants was waived, as the data used in this study adhered to anonymity requirements outlined by institutional protocols and national laws.

Author contributions

XW: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft. XL: Methodology, Supervision, Validation, Writing – review & editing. JS: Data curation, Formal analysis, Validation, Writing – review & editing. MW: Investigation, Supervision, Writing – review & editing. WL: Methodology, Validation, Visualization, Writing – review & editing. XX: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

Free Statistics team given us their unselfish assistance and encouragement.

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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frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 18 March 2024
DOI 10.3389/fneur.2024.1321239

OPEN ACCESS

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RECEIVED 13 October 2023
ACCEPTED 04 March 2024
PUBLISHED 18 March 2024

CITATION
Kawata K, Rettke DJ, Thompson C, Mannix R, Bazarian JJ and Datta D (2024) Effectiveness of biomedical interventions on the chronic stage of traumatic brain injury: a systematic review of randomized controlled trials. *Front. Neurol.* 15:1321239.
doi: 10.3389/fneur.2024.1321239

Effectiveness of biomedical interventions on the chronic stage of traumatic brain injury: a systematic review of randomized controlled trials

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Traumatic brain injury (TBI), in any form and severity, can pose risks for developing chronic symptoms that can profoundly hinder patients' work/academic, social, and personal lives. In the past 3 decades, a multitude of pharmacological, stimulation, and exercise-based interventions have been proposed to ameliorate symptoms, memory impairment, mental fatigue, and/or sleep disturbances. However, most research is preliminary, thus limited influence on clinical practice. This review aims to systematically appraise the evidence derived from randomized controlled trials (RCT) regarding the effectiveness of pharmacological, stimulation, and exercise-based interventions in treating chronic symptoms due to TBI. Our search results indicate that despite the largest volume of literature, pharmacological interventions, especially using neurostimulant medications to treat physical, cognitive, and mental fatigue, as well as daytime sleepiness, have yielded inconsistent results, such that some studies found improvements in fatigue (e.g., Modafinil, Armodafinil) while others failed to yield the improvements after the intervention. Conversely, brain stimulation techniques (e.g., transcranial magnetic stimulation, blue light therapy) and exercise interventions were effective in ameliorating mental health symptoms and cognition. However, given that most RCTs are equipped with small sample sizes, more high-quality, larger-scale RCTs is needed.

KEYWORDS

traumatic brain injury, pharmacology, stimulation, exercise, chronic traumatic encephalopathy

1 Introduction

Despite nearly a century of dedicated research, traumatic brain injury (TBI) remains a significant public health concern, contributing to both morbidity and mortality on a global scale (1, 2). It is evident that the sequelae of TBI are long-lasting, with symptoms persisting for months to years in a majority of patients with moderate to severe TBI (2). Up to 30% of

mild TBI (mTBI)/concussion patients continue to experience symptoms beyond the first month post-injury (3, 4). The timely and accurate diagnosis of TBI is crucial for a prompt recovery, but the impact of appropriate treatment is arguably even more beneficial. Several consensus-based guidelines have been published to guide acute triage and management of TBI (5, 6), but there is a notable absence of universally accepted treatments for the chronic sequelae of TBI, including concussions.

The quality of life remains a vital attribute of individuals grappling with TBI (7). Beyond the evident physical and cognitive disabilities, TBI patients often suffer from psychiatric disorders, encompassing affective, anxiety, post-traumatic stress disorders (PTSD), and sleep disturbances (8, 9). These psychiatric burdens of TBI are largely invisible, yet studies have begun unraveling potential countermeasures for not only physical and cognitive symptoms but also mental health issues stemming from TBI. However, unfortunately, multidisciplinary neurorehabilitation is often inaccessible to the majority of TBI patients. Over the past 3 decades, a myriad of interventions, including pharmacological, stimulation, and exercise-based approaches, have emerged to ameliorate symptoms, such as mental fatigue, and sleep disturbances. For example, Johanson et al. (10) prescribed a four-week course of the stimulant medication (Methylphenidate) to adults experiencing chronic mental fatigue symptoms after a mild to moderate TBI. The results were promising, as Methylphenidate significantly improved mental fatigue symptoms, such as stress, slowness of thinking, difficulty concentrating, and lack of initiative, in a dose-dependent manner. Additionally, other neurostimulants, such as Modafinil (11), Armodafinil (12), and Monoaminergic (13) have demonstrated efficacy as countermeasures for post-TBI fatigue and persistent sleepiness during the post-acute phase of recovery. In a separate randomized controlled trial (RCT), the administration of doxycycline, an antibiotic medication, during the acute phase in TBI patients resulted in significant reductions in the neural injury blood biomarker (neuron-specific enolase) and improvement in the Glasgow Coma Scale over a one-week treatment period compared to a placebo group (14).

In another scope of research, the use of neural stimulation as a therapeutic strategy for TBI has attracted considerable attention. Among these approaches, transcranial magnetic stimulation (TMS) stands out as one of the most extensively explored techniques, designed to elicit repetitive neural activation on the cortical surface with the goal of restoring neural network functionality. Small-scale RCTs implemented repetitive TMS (rTMS) 5 days a week for 2 weeks in patients with mild to moderate TBI. The results indicated that the rTMS intervention was associated with a reduction in pain score and depression symptoms (15, 16), along with improvements in working memory and processing speed (17, 18). However, divergent outcomes emerge from alternative lines of research where the application of rTMS following mild to moderate TBI showed no discernible positive impact on mental health symptoms and demonstrated negligible effects on cognitive function (19) and reducing headaches (20). These conflicting findings, combined with the exploration of other emerging stimulation approach, such as acupuncture and transcranial direct-current stimulation, underscore the necessity for a systematic evaluation of the current landscape of neurostimulant therapy in TBI outcomes, particularly for patients who are living with lingering physical and psychological symptoms.

A groundbreaking study conducted by Dr. John Leddy and his colleagues (21) has played a pivotal role in revolutionizing concussion management through the implementation of a regulated aerobic exercise protocol (22). The early integration of exercise into the recovery process from TBI is thought to stimulate cerebral blood flow (23), trigger the overexpression of neurotrophic factor (e.g., BDNF) to promote neuronal repair (24, 25), and contribute to the regulation of mental health symptoms (26). In a RCT involving adolescents with concussion, individuals assigned to a 20-min daily exercise protocol exhibited significantly faster recovery and a 48% reduced risk of developing persistent post-concussive symptoms (PPCS) compared to their counterparts following a daily stretch protocol (27). These findings were subsequently validated by a recent RCT conducted among adolescents and young adults with concussions (28). While considerable progress has been made in the past decades, leading to promising interventions for TBI, the majority of systematic evaluations for treatment effectiveness has focused on the acute phases of TBI. This underscores a significant knowledge gap and emphasizes the necessity for a systematic review to explore treatment options specifically tailored for the chronic stage of TBI.

This systematic review aims to determine the effectiveness of pharmacological, stimulation, and exercise interventions in alleviating physical, cognitive, and psychiatric symptoms among adult TBI patients experiencing persistent symptoms lasting at least 1-month post-injury. The outcomes of this review aim to offer empirical evidence for individuals grappling with chronic symptoms stemming from various degrees of TBI.

2 Materials and methods

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (29).

2.1 Data sources and search strategy

A systematic review of the current literature was performed by two independent reviewers (DR and CT) using the electronic databases *PubMed, EBSCO*, and *Web of Science*. The search timeframe included studies from 1 January 1990 to 1 September 2020. The following keywords were used in different combinations: traumatic brain injury, TBI, concussion, post-concussion syndrome, persistent post-concussive symptom, post-concussive disorder, treatment, and therapy. For the complete list of combinations, see Table 1. Cited papers within articles meeting the selection criteria were also collected. Searches were limited to RCT, human participants, and English language publications. All records of literature search were examined by title and abstract to exclude irrelevant records. All abstracts that are related to TBI involving treatment or therapeutic interventions were selected for a full reading of the article.

2.2 Inclusion and exclusion criteria

This systematic review included RCTs that evaluate the effectiveness and/or efficacy of treatment or therapeutic interventions for TBI. The scope of this review included pharmaceutical, biomedical,

TABLE 1 Summary of search terms.

Search term	Total	Abstracts reviewed	Articles included
Traumatic brain injury, treatment	965	204	35
Traumatic brain injury, therapy	947	0	0
TBI, treatment	593	3	2
TBI, therapy	580	0	0
Concussion, treatment	139	23	8
Concussion, therapy	140	0	0
Post-concussion syndrome, treatment	59	3	0
Post-concussion syndrome, therapy	59	0	0
Persistent post-concussion symptom, treatment	35	0	0
Persistent post-concussion symptom, therapy	35	0	0
Post-concussive disorder, treatment	14	0	0
Post-concussive disorder, therapy	14	0	0

and physical aspects of interventions/treatments, whereas vestibulo-ocular rehabilitation was not included in this study because of the recent abundance in available systematic reviews and meta-analysis (30–32). Also, homeopathic medicine was not included in this review, given the ongoing debate surrounding its efficacy and safety. This review focuses on TBI in adult civilian population (>18 years old) because the neurodevelopmental rate varies between pediatric patients, and this neurodevelopmental effect makes an interpretation of therapeutic effectiveness difficult. Furthermore, military TBI are often complicated with emergence of PTSD and other psychiatric issues not originated from brain trauma; thus, this review focused on civilian population. Additional exclusion criteria were foreign language papers other than English, conference abstracts, studies that are not RCT (e.g., cohort studies, case studies, animal studies), editorials, magazine articles, and papers that did not fall within the three main topics. Review articles were considered separately and incorporated into the discussion for context.

After the systematic filtration, papers were categorized into the three main domains, which yielded four subareas of interventions per category.

1. Pharmacological intervention focuses on pharmaceutical treatments that included hormone therapy, anti-inflammatory treatment, and neurotransmitter modulation treatment.
2. Stimulation-based intervention uses electrical- or magnetic-based stimulation techniques to excite or inhibit neural signaling, including stimulation techniques like cutaneous, transcutaneous, optical, and transcranial stimulation.
3. Exercise-based intervention aims to increase blood circulation and promote endogenous healing processes, and the interventions range from independent and dependent activities, virtual reality, to an alteration of body temperature.

2.3 Operational definitions

The chronic phase was operationally defined as patients exhibiting persisting signs and symptoms of TBI after 30 days of injury. In this review, the Glasgow Coma Scale (GCS) was used to categorize the initial severity of TBI. The GCS is based on motor responsiveness, verbal performance, and eye opening to appropriate stimuli with scores ranging from 3 being the most severe to 15 being unaffected. A mTBI/concussion is defined by a score between 13 to 15, a moderate TBI from 9 to 12, and a severe TBI from 3 to 8, which represents when the individual is unresponsive. While the majority of papers used GCS to classify the severity of TBI during an admission, this review is focused on papers describing chronic, lingering aspects of TBI at least 30 days from the initial injury. Therefore, the initial GCS score may not accurately reflect the status of patients at the time of intervention. While the Glasgow Outcome Scale (GOS) is the desirable measure in the chronic stage, there was a very large variability between papers in terms of the assessments of neurological status. Regardless of this limitation, the goal of this systematic review was achievable.

2.4 Data extraction and quality assessment

Two authors (DR and CT) independently performed the identification, screening, eligibility and inclusion of studies, with disagreement settled by the senior author (KK). The following was recorded: first author, year of publication, study design, age and number of patients, time since injury, GCS score, treatment methodology, main outcome. When included studies refer to previous papers for details of their methods, full texts of these references were screened, and available data was extracted. In addition, data listed in supplementary documents will also be extracted to present a fully comprehensive review of the literature.

2.5 Risk of Bias selection

The risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (33). The risk of bias was assessed in the context of selection bias (sequence generation and allocation concealment), performance bias (blinding of participants and research personnel), detection bias (blinding of analysis), and reporting bias. The outcomes of the assessment are listed in Supplementary Table 1.

3 Results

3.1 Search outcome

The systematic literature search yielded 1,756 abstracts after filtering for duplicates, and 219 abstracts were assessed and advanced to the full-text review. Following the analysis of 219 full text articles, an additional 175 were excluded. Reasons for exclusions were time-since-injury < 30 days (n =72), nonbiomedical (n=29), age<18 (n=21), not within scope (n=19), military (n=14), and other (n=19). See the study flow chart for details (Figure 1). A total of 44 articles met the inclusion criteria and further categorized into pharmacological (n=19: Table 2), stimulation (n=14: Table 3), and exercise (n=12: Table 4).

3.2 Pharmacological interventions

Nineteen studies were examined involving a pharmacological approach (Table 2). Of those, neurotransmitter-modulation treatments (n = 14) were the most abundant intervention, followed by anti-inflammatory/oxidant (n=2), and hormone therapy (n=2). The main outcome variable was a cognitive function for 10 papers, including working memory, auditory/visual memory, language, and processing speed, whereas the rest of the papers focused on sleep, physical/mental fatigue, or quality of life. Some of the notable findings are that hormone therapy, such as growth hormone (34) and melatonin (Ramelteon) (35), yielded significant improvement in verbal memory, processing speed, psychomotor functioning, and total sleep duration. Similar improvement in cognitive function was

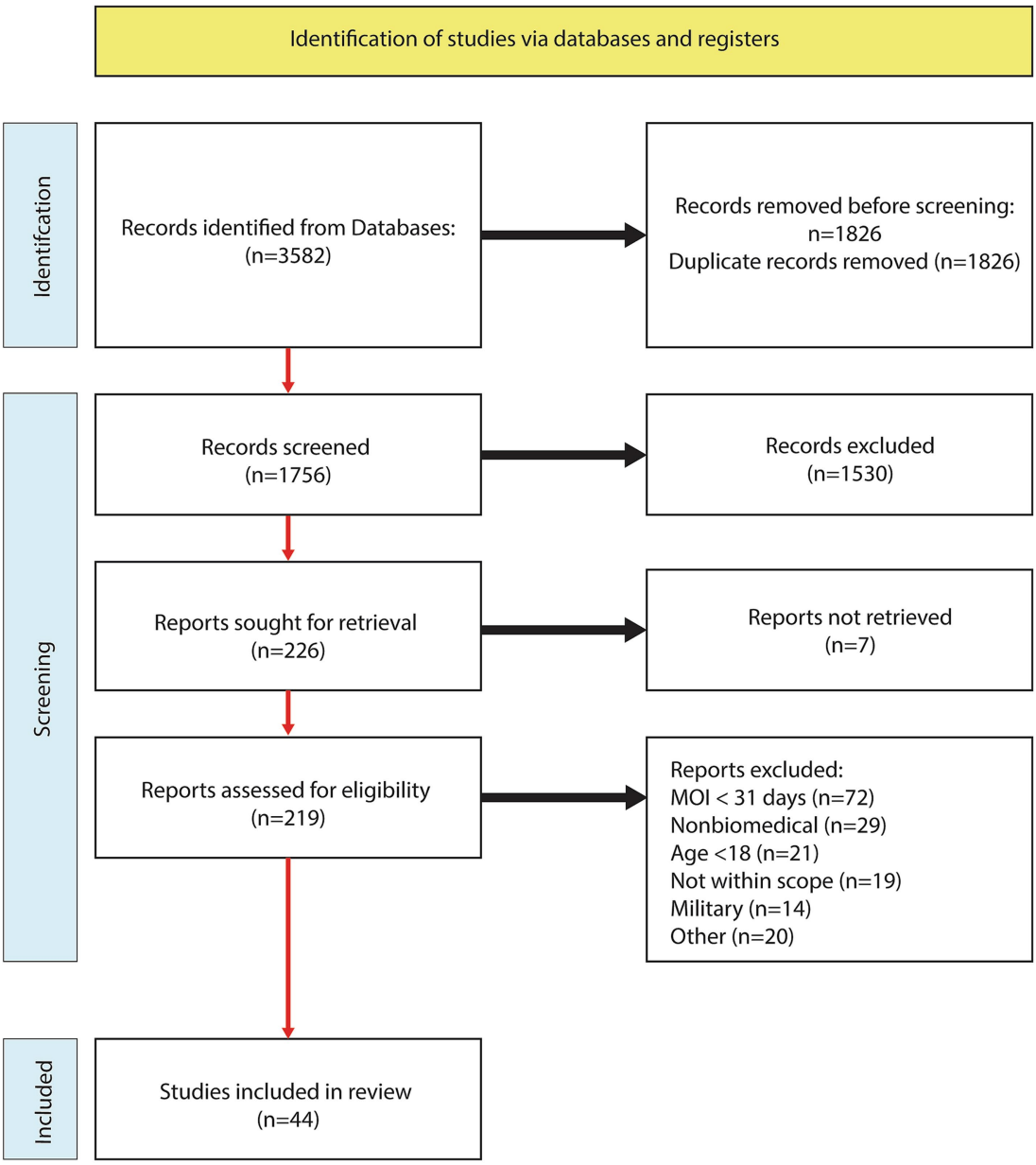

FIGURE 1
PRISMA flow chart.

TABLE 2 RCT using pharmacological interventions.

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Tenovuo (2004)	111 adults with TBI Mild—58% Moderate—10% Severe—32%	71 ± 6.7 months	Central acetylcholinesterase inhibitor (CAI): 27 patients took donepezil once a day (7.2 mg mean), 30 took galantamine twice a day (5 mg mean), and 54 took rivastigmine twice a day (2.3 mg mean). Average duration of the treatment was 18.4 months (6–33 months).	Patient-Reported Outcomes, Glasgow Outcome Scale—Extended	No improvement in self-reported outcomes and Glasgow outcome scale was detected across all 3 treatment types.
Zhang (2004)	18 adults with TBI (the severity ranged from GCS 3–15)	Cross-over design Group A: 4.6 ± 0.7 months Group B: 3.9 ± 0.5 months	Donepezil: A-B vs. B-A design with Donepezil (A) or placebo (B) for 10 weeks each with a 4-week washout period. Dosage was 5 mg/d for the first 2 weeks then 10 mg/d for the last 8 weeks	Auditory Immediate Index (AII), Visual Immediate Index (VII), Wechsler Memory Scale-III, and Paced Auditory Serial Addition Test (PASAR)	Intragroup comparison showed significant increases in AII, VII, and PASAT scores compared to baseline, whereas placebo condition did not change any of the outcomes.
Kim (2006)	18 adults with TBI (no description of the initial TBI severity)	Treatment: 1.6 ± 0.5 years Control: 3.6 ± 3.4 years	Methylphenidate: 20 mg or placebo was given 2 days after baseline then participants were tested 2 h and 2 days post treatment.	Working memory task and endogenous visuospatial attention tasks	The treatment group showed a significant improvement in working memory tasks and visuospatial attention when compared to placebo at 2 h post, but no group difference was found after 2 days.
Silver (2006)	157 adults with mild to severe TBI	Con: 103.4 ± 85.1 months Experimental: 79.9 ± 78.7 months	Rivastigmine: Participants would take 3 to 6 mg/day twice a day or a placebo for 12-weeks	Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing (CANTAB-RVIP) A' subtest and the Hopkins Verbal Learning Test (HVLT)	There were no significant differences in CANTAB-RVIP and HVLT scores between treatment and placebo groups.
Amitabh (2008)	51 adults with TBI Initial severity: Mild: 25.5% Moderate: 23.5% Severe: 51%	Group A: 5.61 ± 4.76 years Group B: 5.95 ± 5.29 years	Modafinil: Subjects were in a 10-week treatment or placebo phase followed by a 4 week washout period and then switched groups for 10 weeks. The treatment consisted of taking 100 mg/day for 3 days, then 100 mg twice a day for 11 days, followed by 200 mg twice a day for 8 weeks.	Fatigue Severity Scale (FSS), and Epworth Sleepiness Scale (ESS)	No significant differences were found between modafinil and placebo in FSS at week 4 or week 10. Modafnil improved ESS score (less sleepy) at week 4 compared to placebo, but no group difference in ESS at week 10.
High (2010)	23 adults with moderate/severe TBI	Con: 5.1 ± 3.6 years Experimental: 11.0 ± 9.2 years	RhGH: Participants took a starting dose of 200 μg/d and increased 200 μg every month up to 600 μg for a year or took a placebo.	Neuropsychological measures: language, visual/spatial functioning, upper extremity motor functioning, information processing efficiency, working memory/attention, learning and memory, executive functioning, intellectual functioning, and emotional functioning	Improvements were found in the treatment group compared to placebo in dominant hand finger tapping test, Wechsler Adult Intelligence Scale III-Information Processing Speed Index, California Verbal Learning Test II, and the Wisconsin Card Sorting Test (executive function)

(Continued)

TABLE 2 (Continued)

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Kaiser (2010)	20 adults with mild to severe TBI	Treatment: 1.8 ± 0.9 years Control: 2.0 ± 1.2 years	Modafinil: Experimental group took 100 mg/day or twice a day if dose was effective and without side effects for 6 weeks, or placebo	Excessive daytime sleepiness (EDS), Epworth Sleepiness Scale, Fatigue Severity Scale	EDS improved significantly when taking Modafinil. There was no difference in posttraumatic fatigue between groups.
Giacino (2012)	184 adults with severe TBI	Experimental: 36–66 days Con: 37–65 days	Amantadine: 100 mg doses were provided twice a day for 2 weeks, doses then increased to 150 mg for week 3, and 200 mg for week 4 if DRS scores did not improve by 2 points in the experimental group. The control group did not receive Amantadine treatment.	Disability Rating Scale (DRS)	Recovery was significantly faster in the treatment group during the 4-week treatment period. However, after the 2-week washout period, the DRS scores became similar between groups.
Johansson (2013)	24 adults with mild/moderate TBI	Patients: 8.6 ± 0.5.1 years	Methylphenidate: Participants underwent three 4-week trials in one of three sequences: (1) no medication, low dose, normal dose, (2) low dose, normal dose, no medication, or (3) normal dose, no medication, low dose.	Mental Fatigue Scale (MFS)	Normal dose of Methylphenidate led to the greatest improvement in MFS score compared to low and no dose. Low dose also showed modest, but significant improvement in MFS compared to the no dose condition.
Theadom (2013)	60 adults with mTBI	Group A: 7.1 ± 2.66 months Group B: 8.04 ± 2.46 months	Enzogenol: 1000 mg of Enzogenol or placebo for 6 weeks, then Enzogenol for 6 additional weeks for all participants followed by placebo for 4 weeks	Cognitive Failures Questionnaire (CFQ), digit span subtest of the Wechsler Adult Intelligence Scale-III, Arithmetic and Letter Number Sequencing of the Wechsler Adult Intelligence Scale-IV	The treatment condition showed a significant reduction (improvement) in self-reported cognitive failures of the CFQ at week 6 compared to the placebo condition. No other outcomes showed significant result.
Menn (2014)	117 adults with severe TBI	1–10 years	Armodafinil: Participants received 50, 150, or 250 mg/day or a placebo dose for 12 weeks.	Multiple Sleep Latency Test (MSLT), Epworth Sleepiness Scale (ESS), Clinical Global Impression-Change (CGI-C) TBI-Work Instability Scale (TBI-WIS), Clinical Global Impression-Severity Illness (CGI-S), and tolerability	Mean sleep latency was significantly improved in the group taking 250 mg/day compared to placebo. ESS and TBI-WIS scores did not show any significant differences between any group comparison.
Ripley (2014)	55 adults with moderate/severe TBI	Experimental: 8.2 ± 6.1 years Control: 6.6 ± 5.5 years	Atomoxetine: Experimental group took 40 mg twice a day for 2 weeks compared to a placebo pill for the control group.	Cognitive Drug Research (CDR) Computerized Cognitive Assessment System	There were no significant group differences in any of the cognitive metrics.
Hammond (2015)	168 adults with moderate/severe TBI	>6 months	Amantadine: 100 mg doses were given twice a day for 60 days for the treatment group, and an equivalent placebo was given to the control group.	Neuropsychiatric Inventory (NPI-I) Most Problematic Item—a scale for irritability assessment	There were no significant improvements seen in either group for NPI-I Most Problematic item.

(Continued)

TABLE 2 (Continued)

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Lequerica (2015)	13 adults with mild/moderate TBI	62.1 ± 91.5 months	Ramelteon: nightly dosage of 8 mg or a placebo for a 3-week period followed by a 2 week washout and underwent alternative intervention for 3 weeks.	Sleep/wake patterns, mood, daytime sleepiness, fatigue, and Neurocognitive Index	Total sleep time and executive functioning had a significant increase in the treatment group compared to placebo.
Berginstrom (2017)	64 adults with mild/moderate TBI	Treatment: 8.58 ± 6.84 years Control: 8.10 ± 7.43 years	Monoaminergic: Experimental group received 5 mg of -OSU6162 twice a day in week 1, 10 mg twice a day in week 2, 15 mg twice a day in week 3 and 4 compared to placebo group.	Fatigue Severity Scale, Mental Fatigue Scale	Both groups showed significant improvements in both outcomes at follow-up and reported no between group differences.
Hart (2017)	32 adults with moderate/severe TBI	Experimental: 53.6 ± 25.1 days Control: 60.2 ± 37.4 days	Dextroamphetamine (DEX): 10 mg or placebo daily for 3 weeks	Rate of functional recovery, attention, engagement in therapy, and mood	DEX did not lead to significant improvement in any functional and cognitive outcomes.
Dorer (2018)	14 adults with moderate/severe TBI	23.43 ± 12.25 months	Methylphenidate: Participants took 30 mg or a placebo 75 min prior to an MRI in counterbalanced order. Scans were on average 2 weeks apart.	Sequential finger opposition fMRI paradigm	Methylphenidate resulted in faster reaction times in patients but was not significant compared to controls. fMFI also found the left inferior frontal gyrus to be activated significantly more compared to when on the placebo.
Theadom (2018)	78 adults with mild/moderate TBI	Treatment: 98 days Control: 94.5 days	NeuroAiD II: Participants took MLC901 0.8 g capsules 3 times a day for 6 months or took a placebo.	Cognitive function assessed by the CNS Vital Signs online neuropsychological test.	The treatment group showed significant improvements in executive functioning and complex attention at 6 months compared to the placebo group.

observed in adults with mild to moderate TBI after a 6-month treatment with NeuroAiD II, which has been shown to promote neurite repair and outgrowth (36). Methylphenidate, which is a stimulant medicine typically used to treat attention deficit hyperactivity disorder, has been used in three RCTs (10, 37, 38). Four-week treatment with Methylphenidate was effective in treating mild to moderate TBI patients who suffered from mental fatigue syndrome (10), whereas acute treatment (1 to 2 days) resulted in transient improvements in working memory, attention, and reaction time, yet the beneficial effects disappeared after 2 days (37, 38). Furthermore, fatigue and daytime sleepiness are common lingering symptoms after TBI, and partial improvements in these symptoms were observed in all levels of TBI after several weeks of treatment with Modafinil (neurostimlant) (11), Armodafinil (neurostimlant) (12), or Monoaminergic (neurotransmitter-inducing medicine) (13). Alternatively, doses of Dextroamphetamine (neurostimlant) (39), Atomoxetine (neurostimlant) (40), or Rivastigmine (neurotransmitter-modulating medicine) (41) did not result in improvements in cognitive function or sleep.

3.3 Stimulation-based interventions

The current review yielded 14 articles focusing on stimulation interventions (Table 3), with TMS as the most popular approach ($n = 8$), followed by transcutaneous and cutaneous stimulations ($n = 4$) and optical stimulation ($n = 2$). As with the pharmacological interventions, all studies set outcome measures on cognitive function, sleep, or mental symptoms including fatigue, except for one study examining electrical muscle stimulation effects on urine retention post-TBI. rTMS intervention demonstrated mixed results. Two studies demonstrated improved outcomes after a 2-week treatment of rTMS, with significantly improved depression symptoms, working memory, processing speed (17) as well as decreased headache burden (15) in patients with mild to moderate TBI. Others demonstrated no discernible positive impact on mental health symptoms and demonstrated negligible effects on cognitive function (19) reducing headaches (20). Similarly, transcranial direct-current stimulation (tDCS), despite receiving consecutive treatments for 15 days, did not result in any improvements in cognition, sleep, and fatigue (42, 43).

TABLE 3 RCT using brain stimulation interventions.

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Schoenberger (2001)	12 adults with mild to moderate TBI	7.71 ± 5.47 years	Flexyx Neurotherapy System: 25 sessions over 5–8 weeks with 6 min of stimulation via LED strobe frequencies in the range of +5 to +20 Hz to a max of 30 Hz, or control condition without Flexyx treatment.	Individualized Symptom Rating Scale, Beck Depression Inventory (BDI), Multidimensional Fatigue Inventory,	Following treatment, participants had an improvement in reports of depression, fatigue, and other symptoms related to TBI.
McFadden (2011)	42 adults with mild/moderate TBI	Experimental: 23.07 ± 3.41 months Control: 25.83 ± 4.24 months	Acupressure: Both groups received eight treatments over 8 weeks. The treatments last 40 min. The control group received treatment in placebo acupoints.	Cognitive impairment and state of being through event-related potentials (ERPs) during Stroop and auditory oddball tasks	Treatment group showed a significant difference compared to the placebo group by having a larger reduction (improvement) in P300 latency and amplitude, as well as a reduced Stroop interference effect. The treatment group showed significantly better performance in working memory task – the digit span, compared to the control group.
Kang (2012)	9 adults with TBI (no initial severity was specified)	216.9 ± 52.5 days	tDCS: (cross-over design) Experimental: transcranial direct current stimulation of 2 mA for 20 min was applied to the left dorsolateral prefrontal cortex. Sham: a dose of 2 mA for 1 min. Participants were tested directly after intervention, 3 h post, and 24 h post.	Level of attention, fatigue, task difficulty, and sleep quality using a numeric scale from 0 to 10.	No statistically significant group differences were found in rating for attention, fatigue, task difficulty, and sleep quality at any post-intervention timepoint.
Zollman (2012)	24 adults with TBI (no description of the initial TBI severity)	Experimental: 2.17 ± 1.27 years Control: 3.00 ± 1.85 years	Acupuncture: Both experimental and control groups met twice a week for 5 weeks with each meeting last 20 min. Experimental group received acupuncture in locations relative for management of insomnia.	Insomnia Severity Index (ISI), Actigraphy, Hamilton Depression Rating Scale (HDRS), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Paced Auditory Serial Addition Test (PASAT)	There was no difference in sleep time between groups but there was a significant improvement in cognitive functioning tested by RBANS and PASAT in the experimental group, whereas no improvement in the control group.
Lesniak (2014)	23 adults with severe TBI	18.1 ± 19.2 months	tDCS: Experimental participants received a tDCS of 1 mA for 10 min to the left dorsolateral prefrontal cortex followed by cognitive training for 15 consecutive days. Control participants received a tDCS for 25 s followed by the same cognitive training for 15 days.	Battery of memory and attention tests	Test scores showed no group differences 3 weeks prior to and immediately before treatment. Following tDCS treatment, the experimental group showed no significant improvements in cognitive outcome measures compared to the controls.

(Continued)

TABLE 3 (Continued)

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Sinclair (2014)	30 adults with self-reported TBI (no description of the severity)	Overall sample: 96 days to 13.35 years (1,106 ± 993 days)	Blue Light: Experimental participants underwent either blue light therapy of 465 nm or yellow light therapy of 574 nm pulses compared to the control group who received no treatment. The treatments lasted for 45 min a day for 4 weeks.	Fatigue Severity Scale (FSS) and Epworth Sleepiness Scale (ESS)	The blue light group showed improvements in fatigue compared to yellow light and placebo. Daytime sleepiness was significantly reduced by the blue light treatment. Self-reported depression using ESS reported no significance.
Choi (2018)	12 adults with mild TBI	Sham: 14.3 ± 7.2 months Experimental: 17.0 ± 7.5 months	rTMS: Experimental group underwent 10 sessions (5x a week for 2 weeks) of TMS at 10 Hz with an intensity of 90% of motor threshold and duration of 5-s, for a total of 20 trains separated by 55-s intertrain pauses to the abductor pollicis brevis muscle area of the precentral gyrus on the affected side. The sham group underwent the same stimulation, but the coil was held perpendicular to the skull, preventing any stimulation.	Therapeutic effects and clinical outcomes including central pain which used the numeric rating scale	The rTMS group showed significantly lower pain scale compared to the sham group after 2 week intervention.
Lee (2018)	13 adults with mild/moderate TBI	Sham: 3.88 ± 1.94 months Experimental: 3.85 ± 1.67 months	rTMS: Each session for the experimental group consisted of 50 trains of 40 pulses on each train separated by 25-s pauses applied at 1 Hz to the right dorsolateral prefrontal cortex. Sham group underwent same protocol without any stimulation to the brain. Participants underwent 30-min sessions 5 days a week for 2 weeks.	Depression using Montgomery-Asberg Depression Rating Scale (MADRS) and cognitive function using the Trail Making Test (TMT) and the Stroop Color Word Test (SCWT)	The experimental group showed significant improvement in MADRS, TMT, and SCWT measures after 2-week intervention. While no group difference in all measures at baseline, the experimental group showed significantly better scores in MADRS, TMT, and SCWT compared to the sham group.
Hoy (2019)	21 adults with mild-to-severe TBI	Con:22.11 ± 13.59 years Experimental: 14.73 ± 10.83 years	rTMS: Experimental group were induced repetitive TMS stimulation to the right and left dorsolateral prefrontal cortex. Right sided treatment included a single train of 1 Hz at 110% of resting motor threshold where left sided treatment was 30 × 5-s trains of 10 HZ with 25-s train intervals at 110% of resting motor threshold. Treatment last for 4 weeks for a total of 20 sessions. Sham group underwent the same stimulation but the TMS coil was held away from skull to prevent stimulation.	Montgomery Asberg Depression Rating Scale (MADRS), Inventory of Depressive Symptomatology-Clinician Rated version (IDS-CR) and Self-Rated version (IDS-SR)	rTMS group showed a significant improvement in working memory and executive function compared to sham group. All participants showed improvements in depressive symptoms regardless of experimental or sham group.

(Continued)

TABLE 3 (Continued)

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Moussavi (2019)	18 adults with mild TBI	Con: 1.6 ± 1.2 Experimental: 1.8 ± 1.4	rTMS: A total of 13 treatment session over the course of 3 weeks were delivered at a frequency of 20 Hz in trains of 30 pulses with an interval of 10 s at 100% of resting motor threshold to the left dorsolateral prefrontal cortex. A total of 25 trains were given at each treatment. Sham group underwent the same treatment length but with no stimulus to the brain.	Rivermead Post-Concussion Symptoms Questionnaire (RPQ3 and RPQ13)	Significant differences were found using the RPQ13 in the group with injuries occurring less than 12 months prior compared to the sham group.
Neville (2019)	30 adults with severe TBI	Experimental: 17.62 months Con: 18.3 months	rTMS: Experimental: Stimulation was applied for 10 consecutive days to the left dorsolateral prefrontal cortex at 10 Hz for 5-s and separated by 25-s of no stimulus for a total of 2,000 pulses each day (50 stimuli/train, 40 trains). The sham group underwent the same protocol but with a sham coil producing no stimulus.	Change in executive function using the Trail Making Test (TMT) Part B	There was no difference in TMT Part B test from baseline to after the 10th day or at 90-day follow-up timepoint between groups.
Siddiqi (2019)	14 adults with mild/moderate TBI	Con:8.1 ± 11.3 years Experimental: 8.4 ± 8.2 years	rTMS: Experimental: Treatment consisted of 20 daily sessions of bilateral rTMS using high-frequency left-sided stimulation of 4,000 pulses at 10 Hz with 5-s trainings and 20-s inter-train intervals followed by a low frequency right sided stimulation of a single train of 1,000 pulses with 1 Hz frequency. Sham treatment consisted of using a coil producing very weak pulses not strong enough to cause stimulation.	Montgomery-Asberg Depression Rating Scale (MADRS), temperament and character inventory (TCI), NIH Toolbox Cognitive Battery, Headache Impact Test	There was no improvement in MADRS, TCI, cognitive battery or headache symptoms in the experimental group after the intervention. No group difference was found.
Zhang (2019)	86 adults with TBI (no initial severity was specified)	Treatment: 8.9 ± 2.4 months Control: 9.1 ± 2.7 months	NMES: 50 Hz frequency, 250 ms pulse duration, 10 s on and 30 s off, 30 min once a week for 8 weeks or placebo	Post voiding residual urine volume	There were no significant differences between the treatment and placebo groups.
Killgore (2020)	32 adults with mTBI	Blue light: 6.8 ± 4.4 months Amber light: 6.7 ± 3.6 months	Blue Light: Experimental participants underwent blue light pulses at 469 nm compared to the placebo group of 578 nm of amber light pulses. Both groups treatment was 30 min a day for 6 weeks.	Actigraphically measured sleep and circadian phase shift, subjective sleepiness, and objective sleepiness. Cognitive function was evaluated by self-evaluated questionnaires and Tower of London (TOL).	Blue light reduced daytime sleepiness and improved executive functioning compared to Amber light treatment.

Optical stimulation therapy, in a form of a 4-to-6 week blue light therapy, has produced significantly reduced daytime sleepiness, fatigue, and depression symptoms compared to controls undergoing yellow or amber light therapy (44, 45). Another type of stimulus, acupressure and acupuncture, for durations of 5 to 8 weeks produced significant improvements in cognitive function, including working

TABLE 4 RCT using exercise-based interventions.

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Jensen (1990)	19 adults with post-traumatic headache	>1 year	Cold Pack: Participants received either manual therapy or cold pack therapy which consisted of 2 rounds of cervical and thoracic mobilization or 2 treatments of a − 14° C cold pack to the neck for 15–20 min. The study lasted 12 weeks.	Pain index for post-traumatic headache	The pain index of the mobilization group at week 5 was significantly lower when compared to the groups using cold packs, as well as pretreatment baseline levels. By week 12 the difference was no longer significant.
Gemmell (2006)	18 adults with mild-to-severe TBI	8.7 years (no SD or range was given)	Tai Chi: Participants attended a 45-min class twice a week for 6 weeks. Controls were placed on a wait-list for a Tai Chi course.	Medical outcome scale short form 36 (MOS SF-36), Rosenberg self-esteem scale (RSES), and Visual analog scales (VAMS)	Tai Chi led to significant improvements on all VAMS scores on 7 mood states (e.g., sadness, energetic, tense) after 6 weeks, as well as between group difference in VAMS. There were no significant differences between groups on the MOS SF-36 or RSES.
Wilson (2006)	38 adults with gait problems due to TBI (No description of the initial TBI severity)	Experimental: 4.0 ± 3.50 months Control: 2.8 ± 1.80 months	Ambulation: Both experimental and control group received physical therapy twice daily for 8 weeks. The experimental group additionally performed 1 h of partial weight baring training twice a week.	Functional Independent Measure (FIM), Functional Assessment Measure (FAM), Standing Balance Scale (SBC), Functional Ambulation Category (FAC), Rivermead Mobility Index (RMI), and Gross Motor Subscale (GMS)	Significant improvements were found in FIM, SBC, FAC, and RMI in both the treatment and control group, with no group difference after 8 weeks.
Blake (2009)	20 adults with mild-to-severe TBI	Con: 14.89 ± 13.62 years Exercise: 16.4 ± 9.04 years	Tai Chi: Intervention participants attended a Qigong exercise class for 1 h per week for 8 weeks. Control participants engaged in non-exercise based social and leisure activities.	General Health Questionnair-12, Physical Self-Description Questionnaire, Social Support for Exercise Habits Scale	Improvements in mood and self-esteem were found after the intervention in the exercise group compared to control at 8-week timepoint.
Driver (2009)	16 adults with TBI Self-reported TBI (no description of the severity)	Treatment: 40.75 ± 14.67 months Control: 36.25 ± 14.17 months	Exercise: Experimental group had 1-h aquatic program 3 times a week for 8 weeks compared to controls 1-h vocational training 3 times a week for 8 weeks.	Profile of Mood States (POMS)	Significant improvements were found between the treatment and control groups for tension, depression, anger, fatigue, vigor, confusion, and friendliness.

(Continued)

TABLE 4 (Continued)

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Hoffman (2010)	76 adults with a history of severe TBI	6 months–5 years	Exercise: supervised 30-min aerobic exercise once a week and unsupervised 30-min aerobic exercise 4 times a week for 10 weeks (treatment) or control	Beck Depression Inventory (BDI)	No significant between-group differences in BDI were found at 10 weeks
Wise (2012)	40 adults with TBI	Total: 2.1 ± 1.4 years	Exercise: Treatment condition (supervised 60-min exercise sessions x1/week, plus unsupervised 30-min aerobic exercises x4/week for 10 weeks).	Beck Depression Inventory (BDI), Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12), Perceived Quality of Life Scale	Exercise treatment led to significantly decreased BDI (improved) from baseline to 10 weeks and from baseline to 6 month-follow-up compared to the control condition. SF-12 mental scores improved significantly from baseline to 10 weeks and baseline to 6 months compared to the control condition.
	Self-reported TBI (no description of the severity)		Control condition with no prescribed exercise session.		
Jacoby (2013)	12 adults with moderate to severe TBI	Experimental: 126 ± 85.33 days	Virtual Reality: Experimental participants received ten 45-min Virtual Reality (VR) treatments 3-4x per week. Total duration of the intervention varied between participants. The control participants received 10 sessions of occupational therapy.	Multiple Errands Tests-Simplified Version (MET_SV) and the Executive Function Performance Test (EEPT)	No improvement was shown in MET-SV and EEPT in either group.
		Con: 100 ± 16.76 days			
Bellon (2014)	69 adults with TBI	100.5 ± 119.9 months	Cross-over design: Walking: 12-week walking program with a pedometer, weekly goals, and an assigned coach. Control condition includes only a nutritional control coach call without walking program.	Perceived Stress Scale (PSS) and Center for Epidemiological Studies-Depression (CES-D)	The 12-week walking intervention led to significant improvements in PSS and CES-D, and such improvements were significantly greater compared to a nutrition-based control group.
	Initial severity:				
	Mild: 15%				
	Moderate: 15%				
	Severe: 52%				
	Unknown: 19%				
Kolakowsky-Hayner (2016)	123 adults with TBI (no initial severity was specified)	97.6 ± 113 months	Walking: 12-week walking program with a pedometer, weekly goals, and an assigned coach. Control condition includes only a nutritional control coach call without walking program.	Global Fatigue Index (GFI), Barrow Neurological Institute (BNI) Fatigue Scale Overall Severity Index Score, Multidimensional Fatigue Index (MFI)	No significant improvement was found in GFI, BNI Total and MFI scores after 12-week walking program.

(Continued)

TABLE 4 (Continued)

Authors (and year)	Population	Time since injury	Intervention (type, dosage, duration, frequency)	Primary outcome measures	Outcome findings
Chiu (2017)	23 adults with TBI Initial severity: Mild: 78.3% Moderate: 13% Severe: 4.3%	27.6 ± 34.8 months	Warm Footbath: In a crossover study, participants were asked to soak their feet in 41°C water for 30 min for 3 consecutive days or continue with usual care (control).	Sleep efficiency (SE), sleep onset latency (SOL), total sleep time (TST), and wake after sleep onset (WASO)	Warm footbath had a significant reduction in SOL and suppressed WASO. There was no difference in sleep efficiency and total sleep time.
Tefertiller (2019)	63 adults with moderate/severe TBI	VR: 8.3 ± 9.2 years HEP: 8.5 ± 7.3 years	Virtual Reality: Experimental participants performed balance exercises 3-4x a week for 30 min for a total of 12-weeks while receiving feedback through VR system (Xbox Kinect). Control participants performed the same balance exercise without VR system.	Community Balance and Mobility Scale (CB&M)	No significant differences were found between VR and Home Exercise Program in CB&M.

memory, comprehension skills, and processing speed, but not sleep duration.

3.4 Exercise interventions

Twelve RCTs using exercise-based therapy investigated the effectiveness of various interventions that aim to promote the healing process by increasing circulation and changes in body temperature (Table 4). There were independent and dependent activity programs ($n = 8$), virtual reality-based activity ($n = 2$), and temperature therapy ($n = 2$). Patients with all severities of TBI and having lingering symptoms for many years benefited from Tai Chi, where 6 to 8 weeks of Tai Chi lessons significantly improved all domains of mood states, such as sadness, energy, happiness, and tension (46, 47). Exercise classes that lasted at least 1 h 3 times a week for 6 to 8 weeks resulted in improvements in symptoms, such as depression, anger, fatigue, vigor, and friendliness in patients with mild to moderate TBI (48, 49). Conversely, a 30-min aerobic exercise for 10 weeks did not alter mental health symptoms in patients with a history of severe TBI. Interventions such as cold-pack therapy, virtual reality, and walking did not improve cognitive function, sleep, or mental health symptoms (50–52).

4 Discussion

Over the past several decades, a vast array of treatments for chronic TBI symptoms have been explored. This systematic review took a novel approach and aimed to evaluate the effectiveness of pharmacological, brain stimulation, and activity-based interventions in the chronic phase (>1-month post) of TBI. There are 4 main findings. First, while many RCTs have used neurostimulant medications to treat physical, cognitive, and mental fatigue, as well as daytime sleepiness, inconsistent results were noted, such that some studies found improvements in fatigue (e.g., Modafinil, Armodafinil) while others failed to realize the improvements after the intervention. Second, in terms of brain stimulation techniques, rTMS showed effectiveness in improving cognitive function and mental health symptoms. Third, blue light therapy induced significant improvements in fatigue and daytime sleepiness in patients with mTBI. Lastly, RCTs outside our scope (e.g., papers published after the search cutoff, 1 September 2020, pediatric TBI) have demonstrated that exercise interventions (e.g., BCTT) may be effective in expediting recovery speed (53–55), especially when an intervention is introduced early on (55). However, RCTs included in this review and using aerobic exercise intervention focused on patients with a history of moderate to severe TBI and indicate that aerobic exercise may not have a strong effect, especially for those who have had a TBI many years ago. Conversely, group exercise like Tai Chi has been shown to improve mental health symptoms.

4.1 Pharmacological interventions

The exploration and characterization of pharmacological interventions have remained a dynamic focus in TBI research since the early 2000s, yielding several medications that effectively enhance cognitive functioning and alleviate fatigue/sleepiness post-TBI. Two articles utilized antioxidative treatments consisting of the administration of MLC901 (NeuroAiD II) (36) and Enzogenol (56). MLC901, rooted in traditional Chinese medicine, exhibited the ability to inhibit cerebral inflammation (57) and promote axonal/dendritic healing and neurogenesis following a TBI (58). Enzogenol is a pine

bark extract with potent modulatory factors against neurodegenerative cell signaling (59). Although MLC901 and Enzogenol have not been tested in severe TBI, RCTs in mTBI patients were able to detect a significant improvement in executive function and complex attention skills, suggesting that these antioxidative compounds may contribute to neuronal cellular healing processes at least in the milder spectrum of injury. Another pharmacological intervention with positive effects on cognitive functioning and sleepiness is Ramelteon (35). Ramelteon is an FDA-approved melatonin agonist medication to treat patients with insomnia and has also been used to explore the effects after a TBI. This drug has an affinity to two different G-protein-coupled receptors, MT_1 and MT_2 in the suprachiasmatic nucleus of the hypothalamus, and regulates the circadian rhythm (60). Following a 3-week nightly dosage of Ramelteon, patients with mild to moderate TBI improved their total sleep time and demonstrated improvements in memory function, psychomotor speed, and cognitive flexibility (35). Of note, in spite of the randomized crossover design, a sample size of 13 patients is underpowered to account for appropriate confounders and potential modulatory factors, warranting a follow-up study with a larger sample size to realize the true effectiveness in post-TBI care.

There were several pharmacological interventions with no promising results, such as Rivastigmine (41) and Atomoxetine (40). Rivastigmine is a cholinesterase inhibitor used to promote mental functioning, including memory and comprehension, and has been used as a treatment for neurodegenerative diseases like Alzheimer's disease (AD). Silver et al. (41) recruited patients with all severities of TBI in the trial; however, 12 weeks of treatment with Rivastigmine did not improve any aspects of cognitive function compared to a placebo group. This discrepancy between AD and TBI patients is likely due to the level of acetylcholine, such that AD patients often have low acetylcholine levels and benefit from Rivastigmine, whereas acetylcholine levels may not be as depleted after TBI as neurodegenerative conditions. As a result, the RCT by Silver et al. failed to realize the effects of Rivastigmine (41). Atomoxetine is a norepinephrine reuptake inhibitor, often used in patients with attention-deficit hyperactivity disorder (ADHD). This medication is used to increase the levels of norepinephrine in the brain by inhibiting its reuptake into neurons. The abundance of norepinephrine is thought to improve the neural signaling to assist in attention, concentration, and impulse control, which are experienced in some TBI patients. Ripley et al. did not observe Atomoxetine's positive effects on cognitive function, perhaps due to either the study was conducted in patients who experienced TBI on average 8.2 years ago or not all TBI patients having chief complaint of inattention and impulse control issues.

4.2 Brain stimulation

Brain stimulation techniques have evolved in the past decade, allowing researchers and clinicians to administer magnetic stimulations (rTMS) to elicit neuronal signaling. There is a sound theoretical basis and clinical utility in treating various neurological conditions, including chronic pain and rehabilitation for stroke and movement disorders (61). However, this systematic review revealed unique patterns and effectiveness of rTMS in TBI care. All but one studies using rTMS set the dorsolateral prefrontal cortex (DLPFC) as their target region of interest, and seemingly sooner the rTMS intervention was conducted post-TBI (regardless of the severity of TBI), the greater the benefit may be for cognitive function (17), chronic headaches (15), and overall symptoms (16). Conversely, rTMS may not be effective in patients with severe TBI (19) and if it is applied years after mild to moderate TBI (avg. 8.4 years) (20). These rTMS data suggest that rTMS may be effective in modulating post-TBI cellular activity, and the effectiveness of rTMS may be influenced by the timing of administration and severity of the initial injury. Nonetheless, all RCTs in this domain are underpowered (n = 9 to 30) to inform a protocol used in clinical settings.

Several therapeutic interventions, such as blue light therapy, acupressure, and acupuncture that can impact the connectivity of the neurosenal network, have yielded beneficial effects. Following 30-min blue light therapy sessions for 6 weeks, patients with mTBI greatly benefited in the context of their cognitive functioning, daytime sleepiness, and fatigue (44, 45). Exposure to blue light, as opposed to amber light, has a positive impact on gray matter volume in the posterior thalamus and greater structural and functional connectivity in the prefrontal cortex and thalamus, which has been shown to be associated with improvements in both cognitive performance and sleep/fatigue (44, 62, 63). Likewise, both acupressure (64) and acupuncture (65) reported significant improvements in cognitive function in patients with mild to moderate TBI, which was partly attributed to the modulation in the limbic-paralimbic neocortical network and subcortical gray matter (65), along with an increased relaxation response (64, 65). Taken together, non-invasive neurostimulation interventions have the potency to facilitate healthy brain network connections, and researchers and clinicians should be encouraged to conduct a larger-scale RCT in patients with chronic TBI symptoms.

4.3 Exercise-based intervention

Exercise-based interventions have been spotlighted in TBI care, owing to the pioneer works (BCTT) done by John Leddy et al. (66). Patients with PPCS often report lingering symptoms including depression, anxiety, and decreased quality of life (49). Despite the RCTs in this review focused on patients with a history of moderate to severe TBI, these RCT results replicated ones from newer RCTs focusing on sports-related mTBI and pediatric mTBI. More specifically, light to moderate exercise or walking, when it is frequent (e.g., 1 h for 3 times a week for 6 to 8 weeks), resulted in improvements in mood, stress, and overall quality of life (48, 49, 67), whereas the shorter duration of exercise (e.g., 30-min per session) and self-guided walking without detailed instruction did not improve any TBI symptoms. This dose and intensity-dependent results may suggest that there is a threshold for inducing positive effects. Exercise interventions during recovery from TBI are aimed not only to increase systemic and cerebral blood flows and regulation of autonomic nerve function, but also to improve cortical connectivity and activation and overexpress brain-derived neurotrophic factor (BDNF). While it is not recommended to engage in high-intensity activity to exacerbate TBI symptoms, reaching certain physiological thresholds may be a key to designing an effective treatment protocol for patients. Although self-guided

movement activity, such as Tai Chi, does not induce the same physiological reaction as walking or running, two RCTs using Tai Chi have shown consistent improvements in patients' mood (46, 47), which is likely through the breathing technique inducing participants to relax and relieve tensions.

4.4 Publication bias

It is important to acknowledge the potential publication bias, often encountered in systematic reviews. This bias occurs when studies with positive or significant findings are more likely to be published, whereas negative or non-significant results may face difficulty in publication. This bias is particularly relevant for smaller-scale pilot RCTs using stimulation- and exercise-based interventions because double-blinding is often infeasible and relative easiness of conducting a pilot RCT due to cost-friendly and less logistical hurdles compared to pharmacological-based RCT, which involves additional layers of regulatory clearance (e.g., FDA). As a result, higher risk of bias was noted especially in the exercise-based interventions (Supplementary Table 1).

4.5 Limitations

While there were several promising candidate interventions, some limitations should be noted to propel future clinical trials. Many, but not all, RCTs had small sample sizes of less than 30 patients with TBI. This trend was prominent in relatively newer interventions (e.g., rTMS, Tai Chi, virtual reality); thus, data from underpowered pilot RCTs should be interpreted with caution. Unlike interventions for acute TBI, research focusing on chronic TBI includes a wide range of patients in terms of time since injury (e.g., 1 month to several years). This introduces other confounding factors, such as lifestyle, occupation, and developmental stages after TBI. Regardless of these potential limitations, some interventions were able to elicit beneficial effects on cognition, mood/mental health, and sleep/fatigue. Initial severities of TBI often determine the procedures for acute triage and care. However, severities of TBI begin to intersect after several months to years, with an example of some moderate TBI patients can recover quickly (68), whereas (68), whereas mild TBI does not mean patients recover patients recover rapidly, in fact some patients can develop lingering symptoms, whereas mild TBI does not mean patients recover rapidly, in fact some patients can develop lingering symptoms for months to years (69). Therefore, initial severities of TBI in the selected RCTs may be less relevant when interpreting the effectiveness of interventions for chronic TBI cases.

4.6 Future directions

TBI is a complex condition that can lead to persistent chronic symptoms lasting for months to even years. Given the high prevalence rates of TBI and its potential implications for later-onset neurodegenerative conditions, there is a crucial need for continuous exploration of effective interventions. Research into candidate pharmaceutical interventions, including neurostimulant medications and growth hormone, would significantly benefit from a more rigorous study design. This entails implementing a more uniform inclusion timeline (e.g., within 3–6 months post-TBI), conducting multi-center trials, and extending follow-up time points. Moreover, gaining a deeper mechanistic understanding through preclinical investigations of these medications can provide valuable insights for the clinical care of TBI patients. Brain stimulation interventions, particularly rTMS and blue-light therapy, necessitate larger sample sizes to replicate previous research findings. This approach aims to determine optimal dosage, intensity, and duration that effectively expedite the recovery process. On a parallel note, exercise-based interventions have gained traction across various health domains, including concussion and TBI care. Despite the relative ease and cost-friendliness of implementing such interventions, there is a need for improved research rigor. Standardizing sessions, dosage, and duration of exercise, along with incorporating physiological parameters to monitor the extent of physiological load, would significantly enhance our understanding of the mechanistic link between exercise intervention and improvements in cognitive and physical symptoms after TBI. While this systematic review focuses on the effects of pharmacological, stimulation, and exercise-based interventions on the chronic phases of TBI, it remains imperative to compare and contrast their effectiveness between acute and chronic phases. This consideration is especially crucial in light of a recent systematic review pointing to the pharmacological efficacy in acute TBI (70).

5 Conclusion

This systematic review revealed several key trends. Several hormone-based (growth hormone, melatonin) and anti-inflammatory/oxidant (Enzogenol, MLC901) medications were associated with robust improvements in executive function, but not mental state or overall TBI symptoms. A series of neurotransmitter-modulation medicines and neurostimulants had inconsistent effects on outcomes, regardless of initial TBI severity. rTMS appears to be a beneficial therapy but its effectiveness is influenced by the timing of administration and severity of the initial injury; the milder the TBI severity and the quicker TMS is delivered, the higher the likelihood of a beneficial outcome. However, given the small sample sizes, a large-scale RCT using the TMS technique is needed. Despite being in the early stages of the investigation, blue light therapy, acupressure, and acupuncture show promise for improved outcomes in chronic TBI patients, whereas tDCS does not seem to have a benefit in this population. Various independent exercise protocols have shown potent effects in improving mood, stress, and overall mental health well-being, encouraging follow-up larger-scale RCTs to confirm previous data from pilot RCTs.

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

KK: Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Funding acquisition, Conceptualization. DR: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. CT: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. RM: Writing – review & editing, Methodology, Investigation, Conceptualization. JB: Writing – review & editing, Methodology, Investigation, Conceptualization. DD: Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was partly supported by National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS) 1R01NS113950 to KK and the Indiana Spinal Cord and Brain Injury Research Fund from the Indiana State Department of Health (SCTBIRF 00055049 to KK).

Conflict of interest

JB reports the interest with Abbott Diagnostics (research support, speaker fees) and BrainScope (research report).

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.2024.1321239/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 10 April 2024
DOI 10.3389/fneur.2024.1363167

OPEN ACCESS

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RECEIVED 29 December 2023
ACCEPTED 02 April 2024
PUBLISHED 10 April 2024

CITATION
Nicolau da Costa LR, Sousa JB, Brito FAC, Igarashi Y, Gomes JMS, Lobão CA, Costa MF, Miquilini L and Souza GS (2024) Color discrimination in fixed saturation level of patients with acute traumatic injury. *Front. Neurol.* 15:1363167.
doi: 10.3389/fneur.2024.1363167

Color discrimination in fixed saturation level of patients with acute traumatic injury

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Introduction: Traumatic brain injury (TBI) is an important public health concern and that may lead to severe neural sequels, such as color vision deficits.

Methods: We evaluated the color vision of 10 TBI patients with normal cognitive function using a color discrimination test in a fixed saturation level. We also analyzed computerized tomography scans to identify the local of the brain damages.

Results: Four TBI patients that had lesions in brain areas of the ventral visual streams, five TBI patients had lesions inferred in brain areas of the dorsal visual stream, and one TBI patient had lesion in the occipital area. All the patients had cognitive and color vision screened and they had characterized the chromatic discrimination at high and low saturation. All participants had no significant cognitive impairment in the moment of the color vision test. Additionally, they had perfect performance for discrimination of chromatic stimulus at high saturation and similar to controls ($n = 37$ age-matched participants). Three of four TBI patients with lesions in the ventral brain and one patient with lesion in the occipital area had impairment of the chromatic discrimination at low saturation. All TBI patients with lesions in the dorsal brain had performance similar or slightly worse than the controls.

Conclusion: Chromatic discrimination at low saturation was associated to visual damage in the ventral region of the brain and is a potential tool for functional evaluation of brain damage in TBI patients.

KEYWORDS

traumatic brain injuries, visual system, ventral stream, visual processing, color vision

Introduction

Traumatic brain injury (TBI) is worldwide public health concern and is the main cause of mortality among different head traumas (1). Survivors of this injury develop permanent neurological sequelae that dramatically affect the quality of life (2). Although cognitive, motor, and sensory deficits are among the main consequences of TBI (3), visual impairments are also a relatively common occurrence (4). TBI can affect visual function through a direct lesion in

cortical areas or in pathways that connect the eyes to the brain (5). Visual functions usually affected by TBI include oculomotor dysfunction, visual acuity impairment, and visual field defects (6). Color vision deficits have been reported to be a sequela of TBI (7–9).

There is a hypothesis regarding the functioning of cortical processing of visual information in which the primary visual cortex receives visual input from the retina and the lateral geniculate nucleus, segregating it into two cortical processing pathways (10–12). One destination for the output information from the primary visual cortex would be the lower regions of the temporal lobe, which exhibit biased processing in object properties enabling conscious perception and recognition (13, 14). This pathway is known as the ventral pathway of the visual system. Another destination from the primary visual cortex would be regions located in the posterior parietal lobe, whose processing is biased towards information related to the spatial location of the object and mediates visually guided motor actions (15, 16). This pathway is known as the dorsal pathway of the visual system. Figure 1 shows schematic illustration, depicting location of presumed ventral and dorsal visual streams.

Several studies have documented that color information is mainly processed by the ventral stream of the visual system (17–19), with important contributions from the ventral occipitotemporal cortex and posterior fusiform gyrus (9, 20, 21). In the cortex, color signals are processed along the ventral pathway from V1–V2 to V4, and Inferior Temporal (TE) region (22, 23). Within each of these areas, studies have shown clustering of color-selective regions (24). However, some investigations have shown that color information plays an important role in a cortical region of the dorsal stream of the visual system (19) and that both visual streams interact and influence one another (10).

Studies have reported that damage to localized regions of the cerebral cortex can lead to cerebral achromatopsia, without significant impairment to other visual aspects (25, 26). Total or partial achromatopsia have been reported following ventral visual system disturbances (27). Patients with TBI experience direct damage to several brain areas and are potentially at risk for developing some degree of cerebral achromatopsia.

Many visual tests have been used to identify cerebral dyschromatopsia (27) such as color naming test, Ishihara plates, and Farnsworth-Munsell 100-hue test (26, 28–30). Shin et al. (31) and Igarashi et al. (32) reported how the use of chromatic discrimination in fixed saturation stimuli can be an alternative for rapid screening of chromatic perceptual losses. In this approach, mosaic arrangements are shown with a target and a background that can only be discriminated based on the chromatic saturation difference between them. Our hypothesis is that patients with TBI located in areas associated with the ventral visual pathway would make a greater number of target identification errors compared to patients with injuries located in cortical areas associated with the dorsal visual pathway. The present investigation reports a case series of chromatic discrimination at fixed saturation levels in 10 patients in the acute stage of TBI.

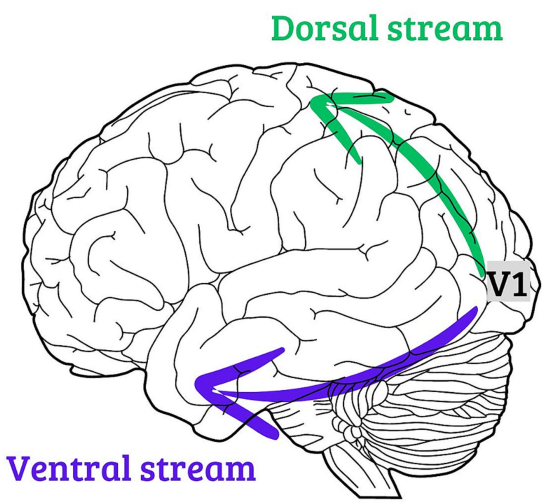

FIGURE 1
A schematic illustration, depicting location of presumed ventral and dorsal streams of the visual pathway.

Methods

Subjects

The sample consisted of 10 TBI patients who attended the Urgency and Emergency Metropolitan Hospital of Belém, Pará, Brazil, a reference hospital for TBI cases. All patients in the present study had no visual complaints before the trauma they sustained or during the period of visual evaluation, and all had visual acuity of at least 20/40. Patient demographic information and the corresponding causes of TBI are summarized in Table 1. Thirty-seven control age-matched participants were recruited (27.8 years old ±7.4), and all had normal fundus and best-corrected visual acuity to 20/20.

All participants provided informed written consent to participate in the present investigation, and all the procedures were approved by the Ethics Committee of the Tropical Medicine Center of the Federal University of Pará (report #2436948).

All TBI patients underwent two screening evaluations using the Mini-Mental State Examination (MMSE) and Ishihara test, and a functional description of their chromatic discrimination using a chromatic discrimination task in fixed-saturation condition. All subjects were binocularly tested. All patients were examined at the time of hospital discharge. The authors also had access to computed tomography (CT) scans of the brain to localize brain area(s) that were potentially damaged.

MMSE

The cognitive function of the patients was evaluated using the MMSE (33). The examination comprised 10 tasks to evaluate spatiotemporal orientation, registration, attention, calculation, recall, language, reading, repetition, writing, and visuomotor skills. The test score ranged between 0 (worst performance) and 30 (best performance). We considered four cut-off levels to classify the severity of cognitive impairment: score > 24 for no cognitive impairment; score between 19–23 for mild cognitive impairment; score between 10–18 for moderate cognitive impairment; and score ≤ 9 for severe cognitive impairment.

Ishihara test

The 2016 book version of the Ishihara test with 14 plates was used to screen for problems suggestive of congenital red-green color vision

TABLE 1 Demographic features of the TBI patients and information of the TBI history of each patient.

Patient	Age (years old)	Sex	Duration from the trauma to the test (days)	Trauma mechanism
P1	28	M	5	Motor vehicle accident
P2	28	F	10	Motor vehicle accident
P3	45	M	7	Motor vehicle accident
P4	45	M	8	Fall from a height
P5	24	M	40	Motor vehicle accident
P6	30	M	23	Assault
P7	30	M	34	Assault
P8	33	M	8	Fall from a height
P9	28	M	18	Fall from a height
P10	34	M	9	Knife stabbing

M: male; F: female.

deficiency. Each plate was shown for 3 s under natural daylight. The participants' task was to indicate the number displayed in the pseudoisochromatic plate. Eight or more errors were considered to represent an altered result (suggestive of dichromacy).

Chromatic discrimination in fixed saturation level

A chromatic discrimination test followed previous published study (32). The test was programmed in MATLAB environment language (R2017a, Mathworks, Natick, MA, United States). A 15″ liquid crystal display was used (color resolution, 8 bits per gun; spatial resolution, 1,366 × 768 pixels; temporal resolution, 60 Hz). The display was gamma calibrated using a colorimeter (CS-100A, Konica Minolta, Osaka, Japan).

The test consisted of a pseudoisochromatic stimulus sequence composed of a mosaic of circles randomly distributed across the display (9.7° × 5.4° of visual angle). Luminance noise was applied in the mosaic, in which 6 values of luminance were linearly distributed between 5 and 25 cd/m^2. A set of circles with chromaticity different from the mosaic field (reference chromaticity: CIE 1976, u' = 0.219; v' = 0.48) composing a squared target (1.5° of visual angle).

The participants' task was to identify where the target was in four alternative positions (up, bottom, left, or right). The test consisted of two stages: pre-test (10 trials); and test (80 trials). In the first 10 presentations (pre-test stage), the chromatic vector of the target chromaticity was 0.07 u'v' units in the CIE1976 color diagram (high saturated chromaticities) and the 10 chromatic axes between 0 and 342 degrees were chosen randomly to paint the target at each trial. It was avoided that axes on the color confusion lines were chosen. These presentations (2 s duration) were used to evaluate whether the patient understood the commands to be tested. The criterion to follow to the next stage of the test was perfect performance in the high saturated colors stage.

In the second stage of the test, the target chromaticity was shown in 20 chromatic axes (0,18, 36, 54, 72, 90, 108, 126, 144, 162, 180, 198, 216, 234, 252, 270, 288, 306, 324, 342, as shown in Figure 1) in the CIE1976 color diagram, chromatic vector of 0.03 u'v' units in the CIE1976 color diagram, and four trials of each of the chromatic axes were performed the. Each presentation of the stimulus had 2 s duration and it was interleaved by a dark screen for 1.5 s. The performance of the task was quantified by the number of errors in the identification of the correct target position. In perfect performance, the error value is 0 and, in the worse performance, the error value is 80. Test duration was about 6–7 min.

Representative examples of the stimulus in the first and second stages of the test are shown in Figure 2.

CT scan evaluation

Conventional CT scans of the head were evaluated by an experienced neurosurgeon to identify the location of brain damage.

Data analysis

To find the cut-off value of the chromatic discrimination performance, we fitted Poisson distribution to the distribution of the number of errors of the control using least mean square method. We considered the 99% percentile in the best fitted binomial function to the data distribution as the cut-off for normal color vision (Normal color vision ≤3 errors, Altered color vision >3 errors). The performance of each TBI patient was compared to this cut-off to be qualified as normal or altered.

Results

Cognitive evaluation

Patient scores on the MMSE ranged between 27 and 30, while all controls demonstrated the maximum score (score = 30) in the examination. TBI patients exhibited more difficulty in executing the visuomotor skills task. The MMSE score of each patient and the task in which they exhibited impaired execution is shown in Table 2 leftmost columns.

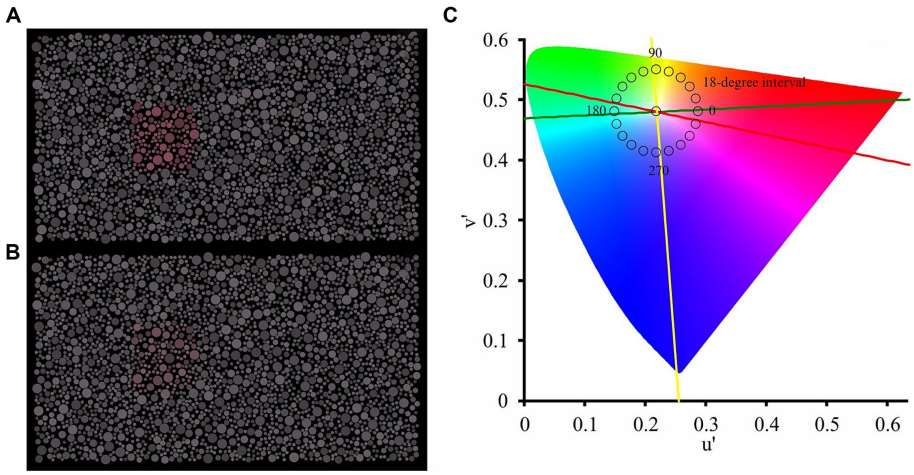

FIGURE 2
Visual stimulation used in the first stage **(A)** and second stage **(B)** of the chromatic discrimination test. The chromaticity of the target was displayed along 20 chromatic axes spaced at 18-degree intervals in the CIE-1976 color space **(C)**. Yellow line represents the titran confusion line, Red line represents the protan confusion line, and Green line represents the deutan confusion line.

TABLE 2 Results of the MMSE for each TBI patient and summary of the results obtained from the different evaluations.

Patient	MMSE score*	Color vision test (errors)	Damaged brain region	Task(s) with error
P1	29	5 (altered CV)	Left occipitoparietal (D)	Visuomotor skills
P2	28	2 (normal CV)	Right frontoparietal (D)	Writing and visuomotor skills
P3	28	2 (normal CV)	Right parietal (D)	Writing and visuomotor skills
P4	30	7 (altered CV)	Right temporal (V)	–
P5	29	1 (normal CV)	Left frontotemporal (V)	Calculus
P6	27	45 (altered CV)	Left temporal (V)	Reading, calculus, and writing
P7	28	52 (altered CV)	Right frontotemporal (V)	Writing and visuomotor skills
P8	29	11 (altered CV)	Left occipital	Visuomotor skills
P9	28	4 (altered CV)	Right frontal (D)	Calculation and visuomotor skills
P10	27	1 (normal CV)	Right frontoparietal (D)	Reading, calculation, and writing

* Normal score; D: dorsal streams; V: ventral streams; CV: color vision.

Ishihara test results

All patients and controls demonstrated perfect performance in the Ishihara test (Table 2).

Brain imaging results

Five patients exhibited lesions in the brain regions belonging to the dorsal visual system (left occipitoparietal region, left parietal region, right frontal region, and frontoparietal region), while four patients exhibited damage in brain areas of the ventral visual system (right frontotemporal region, right temporal region, left frontotemporal region, left temporal region, and right frontotemporal region). One patient had a lesion in the left occipital region, which probably affected both visual streams. The location of brain damage in each patient is shown in Table 2 rightmost columns. CT images of 4 patients are shown in Figure 3.

Chromatic discrimination in fixed-saturation

All patients and controls showed perfect performance on the first stage of the high-saturation color discrimination test, indicating that they all understood how to perform the task. In the second stage of the test, in which the stimuli with low saturation were presented, the performance of healthy participants ranged from 0 to 4 errors, while the performance of traumatic brain injury patients ranged from 1 to 52, as seen in Table 2.

Patients with lesions in cortical areas related to the dorsal pathway exhibited performances of 1, 2 (2 participants), 4, and 5 errors, while patients with lesions in cortical areas associated with the ventral pathway showed performances of 1, 7, 45, and 52 errors. The sole participant with occipital lobe damage made 11 errors in the test.

Figure 4 shows the distribution of the control group (green bars) and the indication of the performance from each patient with inferred dorsal stream lesion (blue arrows), inferred ventral stream lesion (red arrows), and in with occipital lesion (gray arrow).

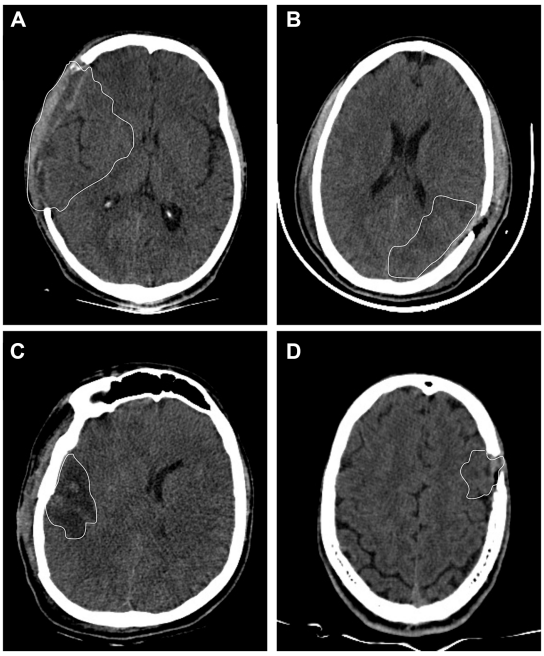

FIGURE 3
Computerized tomography images from 4 TBI patients. **(A)** Patient P6 had left temporal lesion. **(B)** Patient P7 had frontotemporal lesion. **(C)** Patient P1 had left occipitoparietal lesion. **(D)** Patient P3 had right parietal lesion. White lines represent the visible border of the brain damaged area.

All patients in whom the brain lesion was inferred from the dorsal visual system had errors in the normal range (P2, P3, and P10) or had altered vision with errors just above the cut-off for normal color vision (P1 and P9). Three out of four patients with lesions in the ventral visual stream had errors above the cut-off performance of the controls (P4, P6, and P7) and 1 of them had performance in the range of controls (P5). P6 and P7 had the worst performance among all TBI patients. P6 had a color vision loss especially around the deutan color confusion line and P7 had a diffuse color vision loss. The patient with an occipital lesion (P8) demonstrated more errors than the controls.

Discussion

Our main finding was that TBI patients with inferred lesions in the ventral visual system stream exhibited poor performance for chromatic discrimination in fixed-saturation than TBI patients with inferred brain lesion in the dorsal visual stream. Because color is mainly processed by the ventral visual stream, its functional impairment could be a non-invasive indicator of a specific lesion of this neural pathway.

We used a computer-controlled portable test that enabled us to screen several chromatic axes relatively quickly (6–7 min). We used a test that displayed pseudoisochromatic stimulus with fixed saturation at the target. In the first stage of our test, we used highly saturated colors to investigate severe impairment of color vision and the patients' understanding of the psychophysical test what is in agreement with the normal results in Ishihara test. Although this stage of the test is comparable to the Ishihara test, we tested more than red-green vision. This is a first indication of partial color vision loss, since they can discriminate the target in high chromatic saturation. In the second stage of the test, we used a less saturated chromaticity (0.03 u'v' units in the CIE 1976), which was approximately two times higher than the color discrimination thresholds for adults (34, 35). In this stage, we found that the patients demonstrated errors in different chromatic axes, similar to those observed in other investigations (27).

We consider that our results cannot be explained by a lack of patient comprehension of the test commands. The MMSE scores indicated that all patients had normal cognition (36) in the moment of the test execution, and all of them demonstrated perfect performance on the stage of the test that presented target with high saturated chromaticities (0.07 u'v' units in the CIE1976 color diagram). We interpreted that errors in the stage of low saturated chromaticities (0.03 u'v' units in the CIE1976 color diagram) represented an acquired loss of chromatic discrimination.

There is an important debate regarding the existence of a brain area that exclusively processes color information (37–39). The ventral occipitotemporal cortex and posterior fusiform gyrus are brain areas where lesions commonly lead to disturbances of color vision in humans (21, 40). Patients P6 and P7 had the highest error rates in the color discrimination tasks, and their lesions involved the ventral region of the temporal cortex. Patient P8 had the third highest number of errors and had a lesion in the occipital cortex, with probably both streams affected. Patient P4 had the fourth highest number of errors and had a lesion in the right temporal cortex. One case (patient P5) with lesion in the temporal cortex demonstrated good performance in the chromatic discrimination task, and it could suggest that the lesion was possibly anterior to the ventral visual stream. Patients with lesions in the dorsal region of the brain (P1, P2, P3, P9, and P10) performed similarly or slightly worse than the control group.

The number of patients we studied was small and need to be increased to find stronger associations between the location of brain damage and color vision performance. Most similar studies encounter the same limitation; moreover, the study of cerebral achromatopsia is mainly based on case reports or meta-analyses of several different studies (20, 27). Another limitation was that because of the feasibility of application, we implemented the MMSE score as the sole basis to exclude or define cognitive impairment. MMSE is used in clinical setting, however, remains a screening tool rather than a systematic method to diagnose and precisely describe the cognitive impairment, and a much broader battery of tests (including analysis of verbal, executive and memory function, etc.) should be implemented to declare their patients as not cognitively impaired (41). Then, the designation of our patients as having normal cognition should be interpreted with caution.

Our findings suggest that color vision evaluation can be used to assist the diagnosis of functional damage in the ventral visual stream of patients with TBI. The chromatic discrimination test at fixed saturation can be administered quickly and may enable better comprehension of the individual condition of TBI patient's brain.

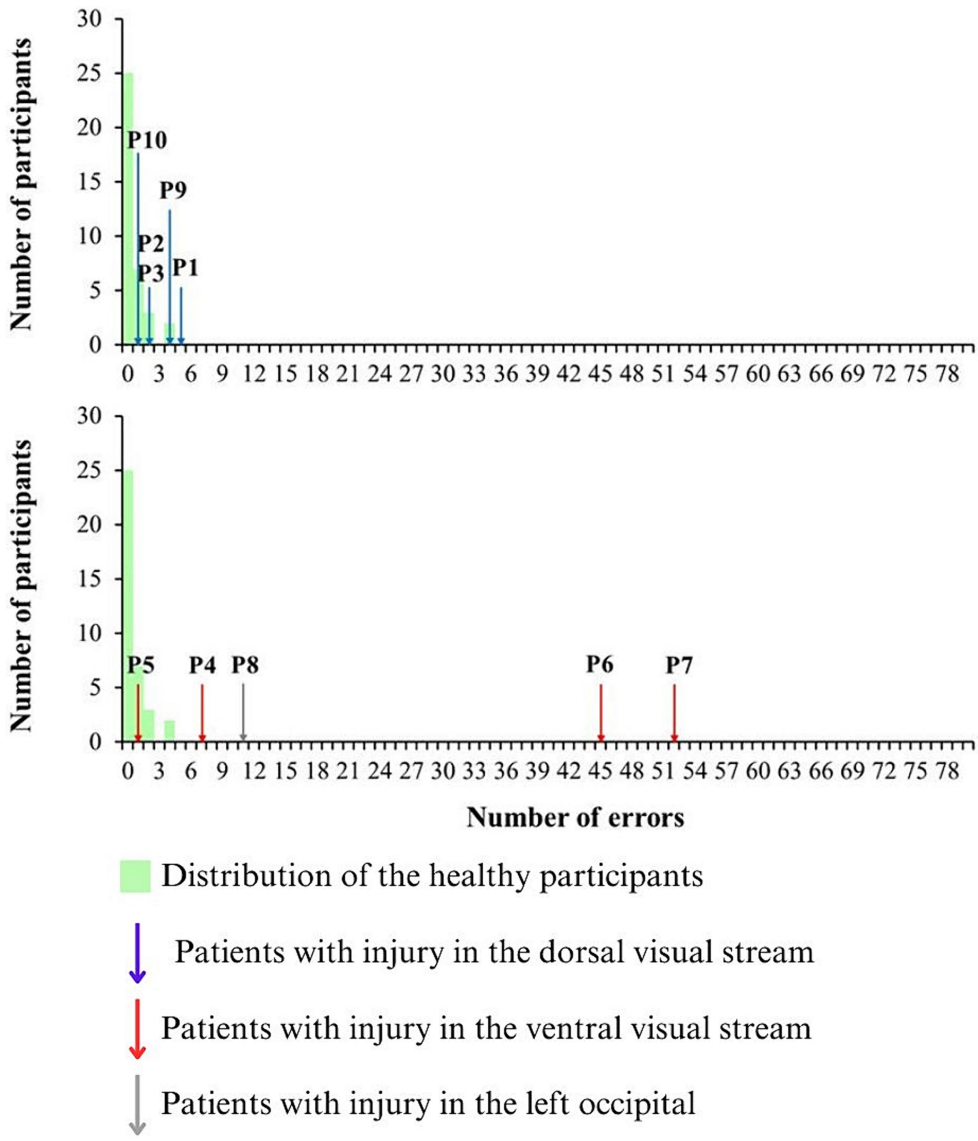

FIGURE 4
Distribution of the errors in the chromatic discrimination test at low saturated stimulus (green bars). The performance of the patients with inferred dorsal brain lesions are indicated by blue arrows, while the performance of the patients with inferred ventral brain lesions are indicated by red arrows. The performance of the patient with occipital lesion is indicated by gray arrow.

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 studies involving humans were approved by Ethical Committee of the Federal University of Pará. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LN: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. JS: Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. FB: Formal analysis, Software, Writing – review & editing. YI: Formal analysis, Investigation, Methodology, Writing – review & editing. JG: Formal analysis, Investigation, Writing – review & editing. CL: Conceptualization, Investigation, Methodology,

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Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from CNPq (#431748/2016-0). GSS and MFC are CNPq fellows.

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 18 April 2024
DOI 10.3389/fneur.2024.1390016

OPEN ACCESS

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RECEIVED 22 February 2024
ACCEPTED 04 April 2024
PUBLISHED 18 April 2024

CITATION
Pyndiura KL, Di Battista AP, Richards D, Reed N, Lawrence DW and Hutchison MG (2024) A Multimodal Exertional Test for concussion: a pilot study in healthy athletes.
Front. Neurol. 15:1390016.
doi: 10.3389/fneur.2024.1390016

A Multimodal Exertional Test for concussion: a pilot study in healthy athletes

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Introduction: Exertional tests have become a promising tool to assist clinicians in the management of concussions, however require expensive equipment, extensive spaces, and specialized clinician expertise. As such, we developed a test with minimal resource requirements encompassing key elements of sport and physical activity. The purpose of this study was to pilot test the Multimodal Exertional Test (MET) protocol in a sample of healthy interuniversity athletes.

Methods: The MET comprises four stages, each featuring three distinct tasks. The test begins with engaging in squats, alternating reverse lunges, and hip hinges (*Stage 1*). The next stage progressively evolves into executing these tasks within specified time limits (*Stage 2*). Following this, the test advances to a stage that incorporates cognitive tasks (*Stage 3*), and the final stage demands greater levels of physical exertion, cognition, and multi-directional movements (*Stage 4*). Heart rate (HR) was obtained during each stage of the MET and participants' symptom severity scores were recorded following each task.

Results: Fourteen healthy interuniversity athletes ($n = 8$ female, $n = 6$ male) participated in the study. HR was obtained for 10 of the 14 athletes (females: $n = 6$, males: $n = 4$). Increases in average and maximum HR were identified between pre-MET and Stage 1, and between Stages 3 and 4. Consistent with the tasks in each stage, there were no increases in average and maximum HR observed between MET Stages 1 to 3. Female athletes exhibited higher average and maximum HRs compared to male athletes during all four stages. All 14 athletes reported minimal changes in symptom severity following each task.

Conclusion: Among healthy athletes, the MET elicits an increase in average and maximum HR throughout the protocol without symptom provocation. Female athletes exhibit higher HRs during all four stages in comparison to male athletes.

KEYWORDS

sport-related concussion, rehabilitation, mild traumatic brain injury, recovery, assessment

Introduction

The clinical assessment of concussion and determination of recovery has undergone remarkable enhancements over the past 30 years (1–6). While post-concussion symptom evaluation continues to be a crucial component (1), clinical evaluation of concussion has evolved to include a variety of tests that now embrace static and dynamic balance, cognitive functioning, oculomotor performance, vestibular functioning, and dual-task proficiency (7, 8). Furthermore, the implementation of a graduated return-to-sport (RTS) strategy has become an essential component of concussion management (1). This strategy involves a graded escalation in physical exertion; the progression through which requires the absence of symptom exacerbation, in accordance with the 2023 Consensus Statement on Concussion in Sport (1).

One significant limitation of our current understanding of RTS following a concussion is the need for universally accepted thresholds for intensity (i.e., heart rate [HR]), type and complexity of movement, and duration of activity required within each stage of the RTS strategy. Presently, providers and patients primarily rely on the subjective response to exertional stressors to guide progression through the various stages. Healthcare professionals must also make decisions based on their patients' recall during each step of the RTS strategy in order to inform further RTS recommendations.

Clinical tests have been developed to mitigate these limitations, purporting to offer a more comprehensive and objective evaluation with consideration of athletic-specific contexts. These tests necessitate the concurrent execution of motor (i.e., physical) tasks with visual or cognitive tasks. These multifaceted "dual-task" testing paradigms have demonstrated a capacity to identify performance deficits potentially overlooked by conventional single-domain clinical measures (9, 10). However, it is essential to underscore that the psychometric properties (e.g., reference norms, test-retest reliability) of these dual-task assessments, as well as the standardization of testing procedures across divergent age groups and cultural norms, have not yet been definitively established (11, 12).

While dual-task tests offer a more accurate approximation of the movements and complexities inherent in sport, there are still limitations as the motor elements employed in such tests typically involve a gait or balance task conducted within a single plane of movement, whereby sports often necessitate multi-planar movements, rotations, and accelerations. Both the Gapski-Goodman Test (GGT) (13) and the Dynamic Exertion Test (EXiT) (14), have bridged this gap by amalgamating sensory, motor, and cognitive components. Both of these tests involve an aerobic exercise component and a plyometric/dynamic circuit protocol (13, 14). When these tests are incorporated within the post-concussion medical clearance assessment, they have demonstrated efficacy in identifying a subset of individuals prone to symptom exacerbation (13, 14). Notably, Marshall et al. (13) found that 14.6% of participants experienced symptom provocation during the GGT or the modified GGT, while Kochick et al. (14) observed that 6.6% of patients exhibited symptom provocation on EXiT.

Despite the significant strides made in concussion management from the utilization of dual-task tests, resource constraints such as the reliance on expensive equipment (i.e., treadmill or stationary bike), extensive spaces, and specialized clinician expertise limit their generalizability. To help address these potential barriers, our objective was to develop a test with minimal resource requirements encompassing key essential elements of sport/physical activity, including HR elevation, multi-planar movement, and multi-tasking; all executable within a limited space such as a doctor's office. The ultimate goal is to develop and validate a generalizable, accessible, user-friendly, and multimodal physical exertion test that captures the key elements of sport participation. By accurately reflecting the multifaceted demands of sport participation, this test is designed to serve as a robust tool in aiding practitioners in the decision-making process for medical clearance, thereby facilitating a safe and informed return to sport for athletes post-concussion. To that end, it is imperative to first ascertain the response of healthy athletes to the Multimodal Exertional Test (MET) to ensure that the test can effectively elicit increases in HR while maintaining symptom provocation to a minimum. Therefore, the purpose of this study was to assess HR responses and associated symptoms at each stage of the MET protocol within a group of healthy interuniversity athletes, thereby establishing a foundational understanding of physiological and symptom responses during exertion.

Materials and methods

Study design

The current pilot study evaluated a newly developed Multimodal Exertional Test (MET) among a sample of healthy interuniversity athletes. The study was completed at an academic institution with all participants providing written informed consent prior to enrollment. All study procedures were in accordance with the Declaration of Helsinki and approved by the Health Sciences Research Ethics Board, University of Toronto (protocol #41884).

Participants

Athletes were recruited during the period from March 2022 through April 2022. Fourteen participants (female, $n = 8$; male, $n = 6$) from seven sports with an average age of 20.0 years old participated in the study. Exclusion criteria for participants included a history of concussion within 6 months of the study assessment and any injuries that would limit the participant from properly performing exercises and/or physical movements, both of which were self-reported. The demographics of the study population are described in the *Results* section.

Measures

Prior to beginning the MET, participants completed the Hopkins Verbal Learning Test (HVLT) (15, 16), a symptom evaluation, and were fitted with a HR monitor. With all prior components included (i.e., HVLT, symptom evaluation, and applying HR monitor to the body), the MET protocol takes approximately 20–25 min to administer and complete.

Multimodal Exertional Test

The development of the MET followed De Vet et al. (17) six-step framework for developing a measurement instrument; details of the process and steps can be found in Supplementary Methods 1. Briefly, the MET consists of a four-stage test with three tasks per stage. The MET progressively increases in difficulty by adding a new component at each stage: (Stage 1) cardiovascular load, (Stage 2) head acceleration,

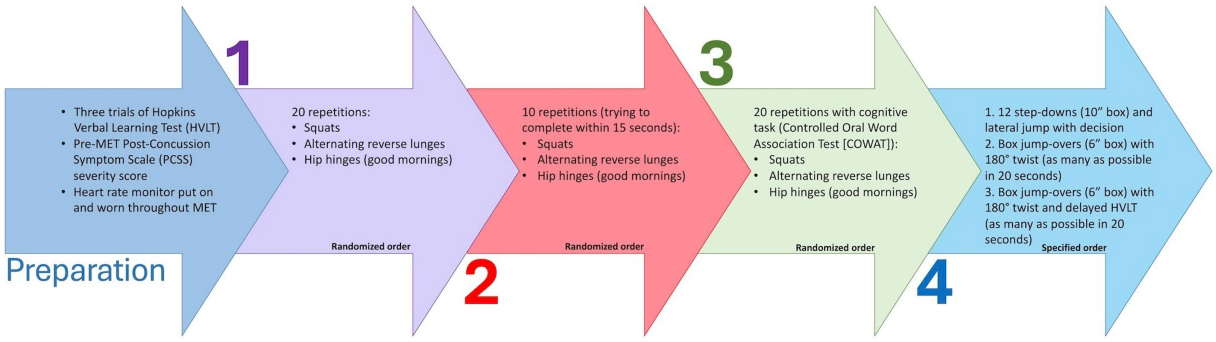

FIGURE 1
Descriptions of preparation prior to and four stages of the Multimodal Exertional Test (MET) protocol. MET, Multimodal Exertional Test; HVLT, Hopkins Verbal Learning Test; PCSS, Post-Concussion Symptom Scale; COWAT, Controlled Oral Word Association Task. Each stage comprises of three tasks in which the order of tasks is randomized for Stages 1–3, however kept in specified order for Stage 4.

(Stage 3) cognitive tasks (i.e., dual-tasks), and (Stage 4) elements of coordination and multi-plane movements (the full protocol can be found in Figure 1).

Hopkins Verbal Learning Test

Three trials of the HVLT (15, 16) were completed before beginning the MET. The HVLT is a 12-word memory test where an examiner reads 12 words at a rate of one word per second and the participant is asked to recite as many words as they can remember. This is completed across three trials with the total number of words calculated (maximum score = 36 words). The delayed recall component was completed during the last task of the MET Stage 4, where participants recited the 12 words from memory (maximum score = 12).

Symptom evaluation

Participants completed a 27-item Post-Concussion Symptom Scale with each symptom ranked on a 7-point Likert scale from none to severe (0 indicated "none," 1–2 "mild," 3–4 "moderate," and 5–6 "severe"). This symptom evaluation comprised of the 22-item SCAT-5 (18) symptom evaluation with an additional five symptoms from the C3Logix platform (19, 20), including "sleeping more than usual," "sleeping less than usual," "difficulty sleeping soundly," "ringing in the ears," and "numbness and tingling." The overall symptom severity score was calculated by summing all rated symptoms (maximum score = 162). Following each task of the MET (12 total tasks), participants were asked if there were any changes to their symptoms and a total symptom severity score was recorded.

Heart rate

Participants placed a Firstbeat chest strap HR monitor (Firstbeat Technologies Oy, Jyvaskyla, Finland) upon arrival and wore it for the duration of the MET. Average and maximum HR were calculated before beginning the MET and during each of the four MET stages.

Statistical analyses

Descriptive statistics were performed for participant demographics. To estimate HR and symptoms across the four stages of the MET, we employed multilevel Student-t models. The modelling was based on the heuristic causal assumption that the MET would elicit an increase in HR without provoking symptoms, and that the estimates of HR and symptoms would differ in males and females. Posterior contrasts were created to estimate the differences across stages and between males and females. Posterior distributions for all estimates were derived using Hamiltonian Monte Carlo as implemented in Stan through RStan (21, 22) (version 2.21) via R (23, 24) (version 4.3). The R packages "rethinking" (25, 26) and "loo" (27) were used to aid in the processing of posterior samples. All models were assessed for convergence by inspection of trace plots, R-hat values, and effective sample sizes. Priors were selected via prior predictive simulation to span a scientifically credible range of outcomes, thus regularizing posterior parameter estimates. For more modeling information, including mathematical notation, prior selection, and posterior predictive checks, please see Supplementary Methods 2 and Supplementary Figures 1–3 and the GitHub repository containing the code accompanying the manuscript.[1] All plots were created using the R packages "ggplot2" (28), "bayesplot" (29), and "tidybayes" (30) and all tables were created using the "gt" (31) and "gtsummary" (32) packages.

Results

Demographics

Participant demographics are reported in Table 1. Briefly, the median age of male (median = 19.1, interquartile range [IQR] = 19.3–20.4) and female (median = 20.1, IQR = 19.3–20.7) participants were similar. Males were on average taller and heavier than females. Males and females also shared a similar concussion history: the majority (males = 62%, females = 67%) reported no prior concussions. Every athlete in the study with a history of concussion had received medical clearance following their most recent incident and was actively engaged in their sport at full capacity. Raw values of MET performance metrics across all four stages can be seen in Table 2.

1 https://github.com/kylap/Pyndiura_et_al_2024_MET_FNeur.git

TABLE 1 Participant demographics.

Characteristic	Female, *N* = 8	Male, *N* = 6
Demographics		
Age	20.08 (19.32–20.68)	19.94 (19.10–20.38)
Height (cm)	164 (162–171)	181 (179–186)
Weight (kg)	65 (63–68)	81 (79–98)
Education Level		
Undergraduate (Year 1)	4 (50%)	2 (33%)
Undergraduate (Year 2+)	4 (50%)	4 (67%)
Sport		
Basketball	1 (13%)	0 (0%)
Field Hockey	2 (25%)	0 (0%)
Football	0 (0%)	3 (50%)
Lacrosse	1 (13%)	1 (17%)
Soccer	3 (38%)	1 (17%)
Track and Field	0 (0%)	1 (17%)
Volleyball	1 (13%)	0 (0%)
Learning Disability	1 (13%)	0 (0%)
Anxiety	2 (25%)	0 (0%)
Depression	2 (25%)	0 (0%)
Headaches/Migraines	1 (13%)	1 (17%)
Number of Prior Concussions		
0	5 (63%)	4 (67%)
1	1 (13%)	2 (33%)
2	2 (25%)	0 (0%)

Data presented as Median (IQR), or *n* (%).

Heart rate

Student-t modeling of HR data showed that the MET elicited an increase in both average HR and maximum HR compared to participants' pre-test values (Figures 2A,B). The first stage elicited an estimated 18.3 beats per minute (bpm) increase in average HR in all participants (90% CI = 15.6–20.6, posterior probability [pprob] > 0 = 100%). There were no meaningful changes in average HR in Stages 2 and 3, while Stage 4 elicited an estimated increase of 18.1 bpm compared to Stage 3 in all participants (90% CI = 15.7–20.4 bpm, pprob = 100%). Similarly, increases in maximum HR were also seen from pre-MET to Stage 1 (est. average increase = 20.2 bpm, 90% CI = 14.8–25.8 bpm, pprob = 100%) and again from Stage 3 to Stage 4 (est. average increase = 27.6 bpm, 90% CI = 22.6–32.3 bpm, pprob = 100%). Average HR in females was an estimated 9.1 bpm higher compared to males (90% CI = −7.7–25.5 bpm, pprob = 82.2%), and maximum HR was an estimated 11 bpm higher (90% CI = −4.7–25.6 bpm, pprob = 87.7%). Raw values for average HR and maximum HR, before and across the four stages of the MET can be seen in Supplementary Tables 1, 2. With the use of the raw maximum HR values, percentages of age-predicted maximum HRs were calculated using the formula of 220—age (33) and can be found in Supplementary Table 3. Briefly, throughout the four stages of the MET, between 55% and 90% of age-predicted maximum HR was achieved. For a table of estimated average and maximum HR in males and females, please see Supplementary Table 4, and for estimated differences across stages, please see Supplementary Table 5.

Symptom evaluation

Prior to beginning the MET, Student-t modeling revealed that females initially reported slightly higher symptoms compared to males (avg. = ~6.3 vs. ~4.8, respectively in females and males; avg. diff = 1.5, 90% CI = 0.1–3, pprob = 93.2%; Supplementary Table 4). Altogether, there were very minimal changes in symptom severity in participants across stages or tasks (Figure 2C; Supplementary Table 5). Raw symptom severity scores for males and females at each stage and task can be found in Supplementary Table 6.

Discussion

The Multimodal Exertional Test (MET) was successfully piloted on healthy interuniversity athletes, demonstrating its ability to incrementally increase and maintain increased HRs across stages without provoking symptoms. Notably, HR increases were observed from pre-MET to Stage 1, and then between Stages 3 to 4, aligning with the expected physical demands of these stages. Female participants exhibited higher HR throughout, indicating a potential sex difference

TABLE 2 Raw values of MET performance metrics.

Characteristic	Overall, *N* = 14	Female, *N* = 8	Male, *N* = 6
Pre-MET			
HVLT (sum of three trials /36)	27 (24–28)	27 (24–28)	27 (25–28)
MET—Stage 1			
20 Hip Hinges (completion time [seconds])	41.6 (36.7–52.5)	48.2 (36.7–56.1)	38.4 (36.7–47.0)
20 Lunges (completion time [seconds])	41.8 (36.5–48.5)	44.8 (37.6–49.7)	40.0 (36.6–41.9)
20 Squats (completion time [seconds])	31.5 (30.5–44.4)	37.1 (30.7–44.4)	31.5 (30.6–41.3)
MET—Stage 2			
10 Hip Hinges (completion time [seconds])	14.7 (13.7–16.2)	15.1 (13.5–16.7)	14.4 (13.8–14.9)
10 Lunges (completion time [seconds])	14.5 (13.7–15.4)	14.9 (14.0–16.4)	14.5 (13.6–14.7)
10 Squats (completion time [seconds])	12.8 (11.9–14.0)	12.9 (12.6–13.9)	12.3 (11.7–14.0)
MET—Stage 3			
20 Hip Hinges + COWAT (completion time [seconds])	36.3 (31.2–41.0)	36.3 (32.4–43.2)	37.2 (28.5–40.5)
COWAT – Hip Hinges (number of words)	7 (5–10)	7 (5–10)	8 (6–8)
20 Lunges + COWAT (completion time [seconds])	39.1 (35.9–41.7)	39.0 (36.9–42.5)	39.1 (33.8–40.1)
COWAT – Lunges (number of words)	7 (5–9)	9 (6–9)	7 (5–7)
20 Squats + COWAT (completion time [seconds])	34.2 (29.3–37.5)	34.7 (33.7–36.9)	29.7 (28.9–36.0)
COWAT – Squats (number of words)	9 (6–11)	9 (6–10)	8 (6–11)
MET—Stage 4			
Step Down + Lateral Jump (number of errors /12)	0 (0–0)	0 (0–0)	0 (0–0)
Jump-Overs 1 (number of jump-overs in 20 seconds)	12 (10–15)	11 (10–14)	14 (11–16)
Jump-Overs 2 (number of jump-overs in 20 seconds)	13 (10–14)	12 (10–14)	14 (12–14)
Delayed HVLT (/12)	10 (8–11)	10 (9–10)	10 (8–11)

Data presented as Median (IQR). MET, Multimodal Exertional Test; HVLT, Hopkins Verbal Learning Test; COWAT, Controlled Oral Word Association Test.

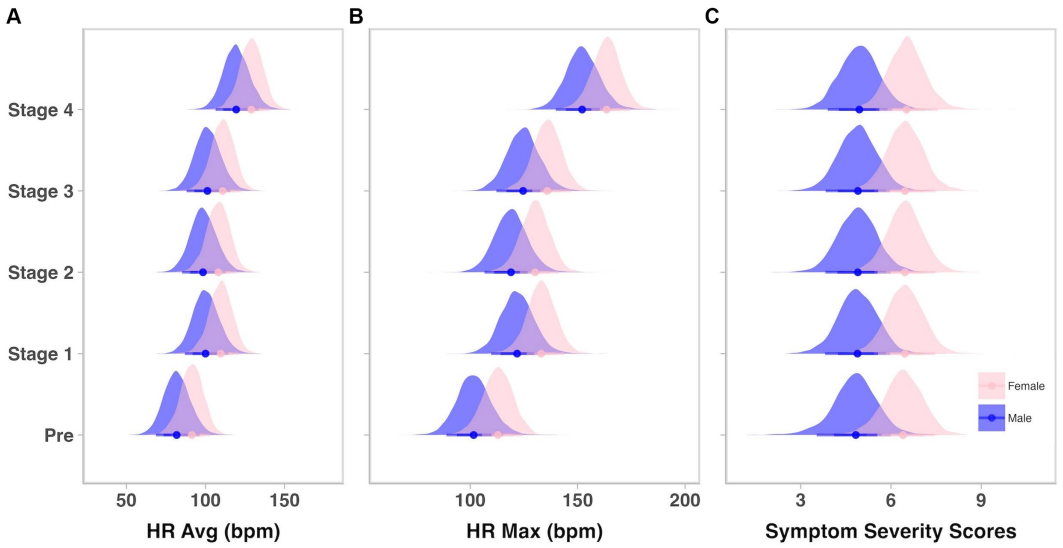

FIGURE 2
Heart rates, but not symptoms, increase across the four stages of the MET. HR, heart rate; Avg, average; bpm, beats per minute; Max, maximum. Density plots displaying posterior distributions of **(A)** average heart rate, **(B)** maximum heart rate, and **(C)** symptom severity scores between males (blue) and females (pink) prior to (Pre) and during each of the four Multimodal Exertional Test stages. Plots were created from 6,000 posterior draws.

in cardiovascular response during the MET protocol. Minimal symptom provocation supports the protocol's safety and provides a normative benchmark for symptom levels in healthy, uninjured athletes.

We monitored average and maximum HR across different stages of the MET protocol. Initial observations indicated that Stages 1 and 4 notably increased HR among participants, likely reflecting a progression from rest to activity in Stage 1, and then an intensification of cardiovascular exertion during Stage 4 through plyometric exercises. The consistent heart rates observed across Stages 1 to 3 were not surprising, as these stages aimed to increase head movement and cognitive load rather than cardiovascular demand.

We observed sex-specific differences in HR response: females exhibited higher and more varied HR than males. These preliminary observations underscore the inherent differences in cardiovascular physiology between sexes (34), and one explanation for these differences may be due to the impact of hormonal variations between sexes, specifically from menstrual cycle or contraceptive use (35, 36). Although the limited sample size precluded a thorough exploration of sex-based disparities, these results provide an intriguing direction for future field testing of the MET protocol.

Understanding how the MET impacts symptom burden in healthy athletes is crucial for differentiating between concussion-related symptoms and those arising from normal physical exertion. Our findings indicate minimal symptom provocation during the MET across all participants, with modelled average symptom severity score estimates prior to the MET and throughout all tasks and stages of approximately 5 for males and 6 for females. These estimates are aligned with prior work in healthy athletes (37), as it is common for individuals to report some symptoms owing to fluctuations in daily stress and well-being. The lack of variation in symptom burden across the MET led to expected degeneracies in our statistical modelling; a larger sample and greater detail of participant information will likely overcome this issue and improve future estimates. However, the consistency of symptom scores holds significant clinical relevance, as it will assist us in identifying clinical cut points for test stoppage and can assist healthcare professionals in both clinical decision-making and the future management of individuals with concussions. More specifically, the minimal symptom provocation in healthy athletes provides normative values that can be used for comparison with the responses of individuals with concussion. This is particularly relevant because symptom provocation may signal incomplete recovery and lack of readiness for individuals to return to sport.

Future directions

Upon completion of the pilot testing and following De Vet et al. (17) six-step framework for the development of a measurement instrument, we reviewed each stage and corresponding tasks to ensure they were aligned with our aim for the MET. The majority of the tasks achieved our desired goals for the stage, however to amplify the cognitive demands of Stage 4's initial task and to further standardize test administration, we have updated the protocol. Instead of a simple step down followed by a lateral jump based on the examiner's hand gesture, we have now introduced a cognitive decision-making component. Participants will now perform a lateral jump to the left or to the right contingent on the color of the card presented to them—red for right, blue for left—thereby elevating the task's cognitive challenge while also standardizing the administration process. Overall, encouraged by the preliminary findings of our pilot work, we embarked on field testing in August 2022. This is the sixth and final step of de Vet et al. (17) framework for measurement tool development and this ongoing process will determine the MET's re-test reliability, validity, and prognostic capability. We envision the MET protocol as an aid for healthcare professionals in monitoring recovery progression and determining an athlete's readiness for returning to sport (i.e., unrestricted game play). The results from the present study have provided the initial groundwork for now pursuing field testing with both healthy athletes and those in post-concussion recovery. Future research stemming from these efforts will illuminate the most strategic moments to employ the MET protocol and its potential added value in clinical settings. Additionally, while the statistical models we derived may be overly complicated for the simple design of the current study, their creation was an important and deliberate step not only for deriving estimates in the pilot phase, but to lay the groundwork for normative data mapping and evaluation of future MET studies where we will be estimating responses within a concussion population throughout clinical recovery and beyond.

Conclusion

The MET has shown promise in its pilot application with healthy athletes, effectively demonstrating the capacity to induce cardiovascular exertion without significant symptom provocation. The MET emerges as an innovative tool that is widely accessible and cost-effective, and may enhance concussion management by integrating cardiovascular stress, cognitive challenges, and coordination tasks with multi-plane movements. This provides a foundation for further validation of the MET and underscores the MET's potential as a multifaceted measurement instrument in the context of sport-related concussion management.

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 Health Sciences Research Ethics Board, University of Toronto (protocol #41884). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. ADB: Data

curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. DR: Conceptualization, Writing – original draft, Writing – review & editing. NR: Writing – original draft, Writing – review & editing. DL: Writing – original draft, Writing – review & editing. MH: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1390016/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Posterior Predictive Check of Student-t model estimating average heart rate. HR, heart rate; Avg, average; bpm, beats per minute. Dot plots facilitating a comparison between the modelled individual average HR predictions (open circles) and the sample data (coloured circles) in males (left panel) and females (right panel) across each stage. Dotted lines represent the estimated group HR averages for males (left panel) and females (right panel). Plots are comprised from 6,000 posterior draws.

SUPPLEMENTARY FIGURE 2
Posterior Predictive Check of Student-t model estimating maximum heart rate. HR, heart rate; Max, maximum; bpm, beats per minute. Dot plots facilitating a comparison between the modelled individual maximum HR predictions (open circles) and the sample data (coloured circles) in males (left panel) and females (right panel) across each stage. Dotted lines represent the estimated group maximum HR for males (left panel) and females (right panel). Plots are comprised from 6,000 posterior draws.

SUPPLEMENTARY FIGURE 3
Posterior Predictive Check of Student-t model estimating symptom severity. Dot plots facilitating a comparison between the modelled individual symptom severity predictions (open circles) and the sample data (coloured circles) in males (left panel) and females (right panel) across each stage and task. Multiple dots with the same colour reflect that each stage is comprised of more than one task. Dotted lines represent the estimated group symptom severity for males (left panel) and females (right panel). Plots are comprised from 6,000 posterior draws.

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 26 April 2024
DOI 10.3389/fneur.2024.1378203

OPEN ACCESS

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RECEIVED 29 January 2024
ACCEPTED 11 April 2024
PUBLISHED 24 April 2024

CITATION
Özen I, Clausen F, Flygt J, Marklund N and Paul G (2024) Neutralization of Interleukin 1-beta is associated with preservation of thalamic capillaries after experimental traumatic brain injury.
Front. Neurol. 15:1378203.
doi: 10.3389/fneur.2024.1378203

Neutralization of Interleukin 1-beta is associated with preservation of thalamic capillaries after experimental traumatic brain injury

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Introduction: Traumatic brain injury to thalamo-cortical pathways is associated with posttraumatic morbidity. Diffuse mechanical forces to white matter tracts and deep grey matter regions induce an inflammatory response and vascular damage resulting in progressive neurodegeneration. Pro-inflammatory cytokines, including interleukin-1β (IL-1β), may contribute to the link between inflammation and the injured capillary network after TBI. This study investigates whether IL-1β is a key contributor to capillary alterations and changes in pericyte coverage in the thalamus and cortex after TBI.

Methods: Animals were subjected to central fluid percussion injury (cFPI), a model of TBI causing widespread axonal and vascular pathology, or sham injury and randomized to receive a neutralizing anti-IL-1β or a control, anti-cyclosporin A antibody, at 30min post-injury. Capillary length and pericyte coverage of cortex and thalamus were analyzed by immunohistochemistry at 2- and 7-days post-injury.

Results and Conclusion: Our results show that early post-injury attenuation of IL-1β dependent inflammatory signaling prevents capillary damage by increasing pericyte coverage in the thalamus.

KEYWORDS

traumatic brain injury, interleukin-1β, cytokine, pericytes, platelet derived growth factor (PDGFRβ), capillaries

Introduction

Traumatic brain injury (TBI) is a heterogeneous disease with complex pathological mechanisms that consist of primary and secondary brain injury. The primary brain injury is caused by a mechanical force transmitted to the brain that can disrupt network function and results in a long-lasting secondary injury in connected remote areas (1). The process of secondary injury includes neuroinflammation, vascular and white matter changes, and blood brain barrier (BBB) dysfunction (2–4). Diffuse injury to white matter tracts and the vasculature in deep grey matter regions such as the thalamus, a region particularly vulnerable to TBI in both humans and rodents (5–7) contributes to post-traumatic morbidity.

The inflammatory response in the brain after diffuse TBI has been previously reported, which could be closely linked to a variety of pro-inflammatory cytokines (8, 9). Among them, Interleukin-1 beta (IL-1β) is a major pro-inflammatory cytokine produced in the brain by activated resident microglia, astrocytes, and endothelial cells (10–12) that acts through binding to its cell surface receptor IL-IR (12–14). Both moderate and severe TBI leads to increased levels of IL-1β mRNA and protein in the cortex and deep central brain structures, observed as early as 1 h post-injury (15, 16). This rapid production of IL-1β is involved in neuroinflammatory processes associated with neurodegeneration (11, 17).

Cerebral autoregulation (CA) maintains a consistent and adequate blood flow to the brain when the cerebral perfusion pressure (CPP) fluctuates (18). Adequate cerebral perfusion and oxygen delivery are crucial for early stages of TBI as reductions in cerebral blood flow (CBF) may lead to secondary pathologies and poor clinical outcome (19). Upon TBI, the release of inflammatory factors and the activation of immune cells can affect the cerebral vasculature (9, 20, 21). Consequently, the vascular inflammatory pathways could be a putative mechanism compromising the CBF, ultimately resulting in dysfunction of cerebral autoregulation (CA) (22). A few experimental studies using fluid percussion models demonstrated that acute post traumatic hypoperfusion is associated with disrupted microvascular integrity and decreased capillary density (23–25). Most importantly, a functional capillary network depends on dynamic changes in pericyte distribution and morphology coordinated across the capillary network (26). Given that pericytes are highly susceptible to brain injury and ischemia, any disruption of the crosstalk between pericyte and the vascular wall of capillaries (27, 28) can lead to pericyte malfunction and capillary degeneration during the subacute phase of brain injury (29, 30). Cerebrovascular injury is another common observation closely linked to inflammation in experimental TBI models (3, 25, 31). Since IL-1 receptors are expressed in both endothelial cells and pericytes, it is likely that the cerebrovasculature is a key target for inflammatory signals, including IL-1β (32). However, possible effects of IL-1β on the regional capillary network along with the pericyte response after TBI remain unclear.

The behavior analyses from our previous TBI studies in rodents indicate that concomitant changes in white matter structural integrity accompanied the alterations in functional connectivity between thalamocortical regions (20, 33, 34). Indeed, diffuse TBI can lead to motor deficits in rodents due to brain network dysfunction and damage to the thalamus, which gradually leads to neurodegeneration over time (35, 36). It has been suggested that post-injury inflammation may play a significant role as a secondary injury mechanism, both for the vasculature and for deep brain structures (9, 20, 37). IL-1β neutralization can reduce brain tissue loss and improve visuospatial learning and memory associated with thalamocortical regions in mouse models of brain injury (20). However, the underlying mechanisms by which IL-1β affects brain injury in these regions and vascular dysfunction are not yet fully understood. Therefore, we further hypothesized that post-injury inflammation may be a key secondary injury mechanism both for the vasculature and for deep brain structures such as the thalamus. To test this hypothesis, we used the central fluid percussion (cFPI) model in mice and investigated whether neutralizing IL-1β attenuates capillary damage by modulating pericyte morphology and number in the cortex and thalamus.

Materials and methods

Surgical procedure

This study utilizes tissue samples from a prior study with other objectives (33, 37) in line with the guideline principles at Karolinska Institute, with the aim to improve the ethical use of animals in testing according to the 3R principle. The total number of included animals in the study was 58 out of total 116 mice.

In the two-days post injury (dpi) group, the number of included animals per group was sham+CsA ($n=3$), sham+IL-1β ($n=3$–4), cFPI+CsA ($n=5$), and cFPI+IL-1β ($n=4$–5). In the seven-dpi group, the number of included animals per group was sham CsA ($n=3$), sham+IL-1β ($n=3$–4), cFPI+CsA ($n=4$), and cFPI+IL-1β ($n=5$). In the current study, we have analyzed the brains at 2 and 7 dpi, which were strategically selected based on previous findings and the functional outcomes of interest (20, 33, 35, 37).

Adult male mice C57BL/6 mice (pre-injury weight 25 ± 1.7 gram; Taconic, Denmark), were housed with free access to food and water for a minimum of 7 days prior to surgery. Seventy-eight C57BL/6 mice were subjected to cFPI as described previously (33, 37). Briefly, after making a craniotomy over the midline midway between the bregma and lambda sutures, a plastic cap was placed on it. The dura mater was kept intact. The saline cap filled with isotonic saline was attached to the Luer-Lock on the fluid percussion device (VCU Biomedical Engineering Facility, Richmond, VA). TBI was performed releasing the fluid percussion pendulum to strike a saline-filled cylinder in order to create a pressure wave transmitted into the closed cranial cavity. Thirty-eight sham-injured animals were subjected to an identical procedure as the cFPI animals except that the pendulum was not released.

IL-1β neutralizing antibody administration

The mouse-specific IL-1β neutralizing antibody (01BSUR, 300 μg/dose) or as control, anti-cyclosporin A mIgG2a (CsA-Ab; 500 μg/dose) (kindly provided by Novartis Pharma AG, Basel, Switzerland) were administered intraperitoneally (ip) 30 min after sham injury or cFPI for all evaluated groups (33, 37). The antibody solutions were mixed with normal saline to obtain a 75 μg/mL concentration. Each mouse was administered 0.15–0.2 mL of the diluted solution, resulting in a dosage of 500 μg/kg.

Tissue preparation

The mice were sacrificed at 2 and 7 dpi and transcardially perfused using 4% formaldehyde (HistoLab Products AB, Gothenburg). The brains were postfixed overnight at 4°C and placed in 30% sucrose solution. Brains were cut at 20 μm thickness, and all sections were stored in cryoprotectant buffer [30% glycerin, 30% ethylene glycol, and 40% 1x phosphate buffered saline (PBS)] at −20°C.

Immunohistochemistry

Free-floating brain coronal sections were washed three times in phosphate buffer saline (PBS), brain sections were then blocked in 5%

normal donkey serum (NDS) in PBS supplemented with 0.25% Triton X-100 (PBS-T) for 1 h. Primary antibodies were incubated overnight at room temperature or at 4°C in 3% NDS PBS-T. The following primary antibodies were used: for labeling pericytes anti- PDGFRβ (rabbit, 1:100, Cell Signaling, Danvers, United States), for blood vessel staining anti-podocalyxin (PODXL) (goat; 1:400, R&D Systems, Minneapolis, United States). For PDGFRβ detection, sections were subjected to heat-induced antigen retrieval in citrate buffer for 30 min at 80°C.

For brightfield staining of PDGFRβ, brain sections were quenched with a peroxidase solution (3% H_2O_2, diluted in PBS) for 15 min prior to blocking. After incubation with the primary antibody, sections were incubated with the corresponding anti-rabbit biotinylated secondary antibody (1:500, 711-065-152, Jackson Immunoresearch, Baltimore, United States), in 3% NDS PBS-T, at room temperature for 2 h, and the signal was enhancement by using Vectorstain ABC Elite kit (Vector Laboratories, CA, United States). Staining was revealed using chromogen 3,3-diaminobenzidine-tetrahydrochloride (Dabsafe, Saveen Werner AB, Limhamn, Sweden) and 3% H_2O_2. Sections were dehydrated in consecutive higher concentrations of ethanol, followed by xylene and mounted using Pertex (Histolab AB, Gothenburg, Sweden).

For immunofluorescence, after incubation with primary antibodies, sections were washed in PBS and incubated with fluorophore-conjugated secondary antibodies for double labeling of PDGFRβ and PODXL The secondary antibodies were used: CY2-conjugated donkey anti-rabbit (1:500, 711.225-152, Immunoresearch, Baltimore, United States) for PDGFRβ and Daylight 649-conjugated donkey anti-goat (1:500, 705-495-147, Immunoresearch, Baltimore, United States) for PODXL.

Brightfield image processing and pericyte quantification

Sections stained with 3,3′-Diaminobenzidine (DAB) were analyzed using Olympus BX51 light microscope and cells counted using CellSens digital imaging software. Figures were composed using Photoshop CS5 software. To quantify the number of DAB-stained PDGFRβ$^+$ pericytes, cells were identified by their typical pericyte morphology and counted manually in both the somatosensory cortex and the thalamus using CellSens digital imaging software (from AP −1.06 according to Bregma). Four optical fields of 0.5mm^2 from each brain region were analysed at 20×. Three coronal sections, including the thalamus, were analyzed between −2.30 and −2.56 mm from bregma for each mouse.

Pericyte coverage and capillary length

Pericyte capillary coverage was determined as the percentage of PDGFRβ$^+$ pericytes surface area covering total PODXL$^+$ capillary surface area per field (ROI) (224 × 224 μm) in the somatosensory cortex and thalamus. A maximum projection of 15 micrometer z-stacks was acquired from both the somatosensory cortex and thalamus section (from −1.06 according to Bregma) using a Zeiss LMS510 confocal microscope. A coronal section, including thalamus, was analyzed − 2.30 mm from bregma for each mouse. Four images of the somatosensory cortex and two images for the thalamus were obtained at 40X. The areas of PDGFRβ$^+$ pericytes and PODXL$^+$ blood vessels from capillaries defined by ≤10 μm diameter were separately subjected to threshold processing and the respective signal for each image was calculated using the NIH Image J Area Measurement tool.

For measurement of the total capillary length, the maximal projection of images at 40× magnification (Zeiss LMS510) was obtained for each section and capillary length assessed using the NIH Image J software, NeuroJ plugin tool (38). Briefly, PODXL-positive capillaries were subjected to threshold processing and a binary picture was created. Each capillary was outlined manually with the freehand line tool allowing to capture varying vascular shapes as previously described (38).

Statistics

Graphs and statistical analysis were made with Prism v.8 (GraphPad Software). Since the study utilizes tissue samples from a prior study with other objectives, power analyses were initially performed according to those previous studies to estimate the effect of neutralizing IL-1β antibody. However, we had previously observed an approximately >60% decrease in the pericyte coverage from cFPI in preliminary experiments, which suggested a group size of $n = 4$ to be sufficient to detect the hypothesized difference when applied to the current study.

Shapiro–Wilk normality test was used to analyze normality of data distribution. Two-way ANOVA followed by Tukey post-hoc multiple comparison tests was performed. The normally distributed data were presented as mean ± standard deviation (SD). Significance was set at $p < 0.05$.

Results

Early effect of neutralizing IL-1β antibody on maintenance of capillary length in the thalamus is correlated with increased pericyte coverage after diffuse TBI

In the thalamus, cFPI + CsA Ab resulted in a more than 20% decrease in the total capillary length as compared to the sham-injured mice treated with CsA + Ab at 2 and 7 post-injuries (dpi) (2 dpi, $p = 0.003$) (Figures 1A,B); 7 dpi ($p = 0.020$) (Figures 2A,B). This reduction in capillary length was completely normalized by neutralizing anti-IL-1β antibody treatment to levels comparable to those observed in the sham CsA + Ab group both at 2 dpi ($p < 0.0001$) (Figure 1B) and 7 dpi ($p = 0.0005$) (Figure 2B).

To determine changes in pericyte coverage, we examined pericytes processes in relation to endothelial cells forming the microcapillary wall (Figures 1–4). PDGFRβ$^+$ pericytes were identified by their prominent cell body and processes, and their perivascular location adjacent to PODXL expressing blood vessels was confirmed. We observed varying degrees of pericyte coverage in response to the cFPI injury and neutralizing antibody treatments (Figures 1–4). There was loss of PODXL$^+$ expression in capillaries in areas where pericytes coverage was completely or partially absent in the thalamus of cFPI mice receiving control CsA Ab treatment (Figures 1, 2). At 2 dpi, cFPI

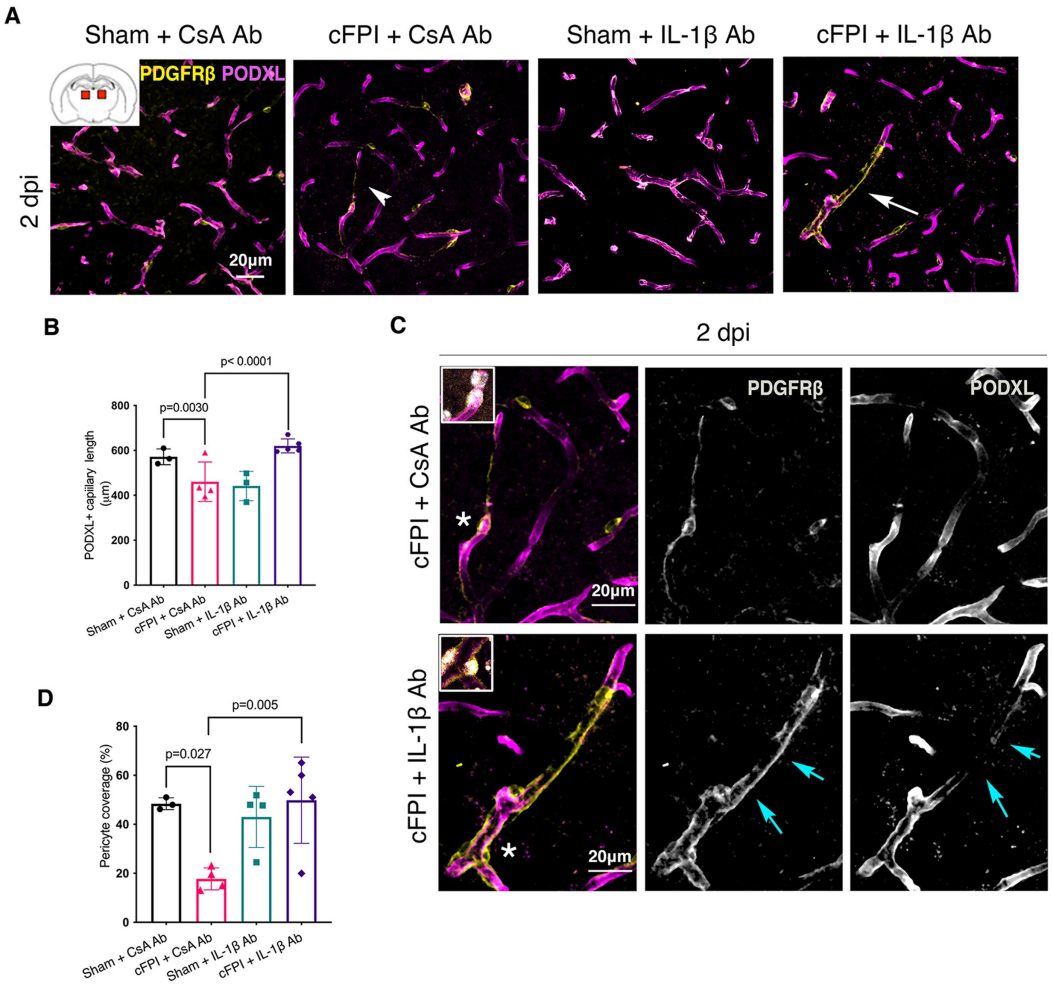

FIGURE 1
IL-1β neutralization increases pericyte coverage and capillary length in the thalamus at 2 dpi. **(A)** Representative confocal images showing podocalyxin$^+$ (PODXL) capillaries (magenta) and PDGFRβ$^+$ pericyte coverage (yellow) in the thalamus at 2 dpi. **(B)** Quantification of total capillary length (sham + CsA, $n = 3$; cFPI + CsA, $n = 4$; sham + IL-1β, $n = 3$; cFPI + IL-1β, $n = 5$; mean ± SD) in the cortex at two after the injury. **(C)** High magnification confocal images showing morphology of pericytes in cFPI + CsA Ab (upper panel, white arrow head in **A**) and cFPI + IL-1β Ab group (lower panel, white arrow in **A**). Coverage by PDGFRβ$^+$ pericytes in cFPI + IL-1β Ab group, indicated by cyan arrows. Boxed areas show cell nuclei of a pericyte stained with DAPI (grey). **(D)** Quantification of PDGFRβ$^+$ pericyte coverage (sham + CsA Ab, $n = 3$; cFPI + CsA Ab, $n = 4$; sham + IL-1β Ab, $n = 4$; cFPI + IL-1β Ab, $n = 5$; mean ± SD).

caused ca 65% decrease ($p = 0.027$) in PDGFRβ$^+$ pericytes coverage in the thalamus (Figures 1A,D). The cFPI group treated with neutralizing IL-1β antibody, however, reached sham control values and had significantly higher pericyte coverage than the cFPI + CsA Ab control group ($p = 0.005$) (Figures 1A,C,D). Unlike at 2 dpi, cFPI did not cause significant changes in coverage of PDGFRβ$^+$ pericytes when compared to sham-operated mice at 7 dpi in the thalamus (Figures 2A,C,D).

Neutralization of IL-1β results in higher pericyte coverage in the cortex after diffuse TBI

In the cortex, there was no significant difference in the capillary length at 2 dpi between groups (sham + CsA Ab and cFPI + CsA Ab) ($p = 0.416$); CsA Ab and cFPI + IL-1β Ab ($p = 0.094$) (Figures 3A,B). In the brain injured group, loss of PODXL$^+$ expression in capillaries was found in areas where pericytes coverage was completely or partially absent (Figure 3C, upper panels). While there was no reduction in capillary length, the cFPI resulted in a 50% decrease ($p = 0.036$) in pericyte coverage when compared to the sham group at 2 dpi (Figure 3D). Pericyte coverage was 47% higher in neutralizing IL-1β antibody antibody-treated mice then in the injured group that received only control antibody (CsA Ab) at 2 dpi ($p < 0.0001$) (Figures 3C,D).

At 7 dpi, the total capillary length in the cFPI + CsA Ab group was similar to the sham-injured mice treated with CsA Ab ($p = 0.573$) (Figure 4A). Although the capillary length of cFPI + IL-1β Ab-treated mice was higher and comparable to sham-values, it did not reach statistical significance when compared to the cFPI + CsA Ab group ($p = 0.095$) (Figures 4A–C). However, the brain injured mice that received neutralizing IL-1β antibody had significantly higher pericyte coverage than cFPI + CsA Ab group ($p = 0.021$) (Figures 4C,D), whereas pericyte coverage was not altered in cFPI + CsA Ab mice compared to the sham-injured CsA Ab group at 7 dpi (Figures 4A,D). There was significant difference between sham + CsA Ab and sham + IL-1β groups ($p = 0.002$) (Figure 4D).

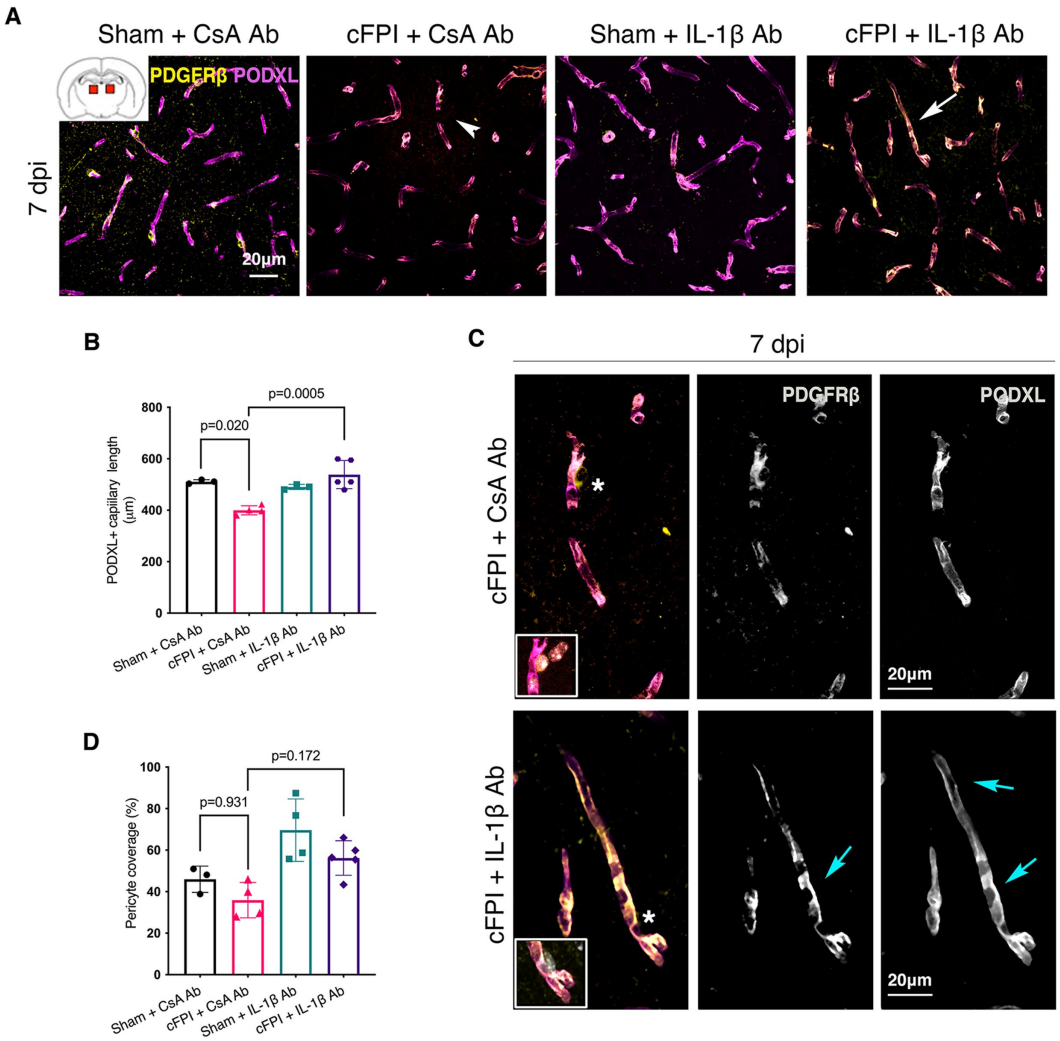

FIGURE 2
IL-1β neutralization increases only capillary length in the injured thalamus at 7days post-injury. **(A)** Representative confocal images showing podocalyxin⁺ (PODXL) capillaries (magenta) and PDGFRβ⁺ pericyte coverage (yellow) in the thalamus at 7 dpi. **(B)** Quantification of total capillary length (sham + CsA, *n*=3; cFPI + CsA, *n*=4; sham + IL-1β, *n*=3; cFPI + IL-1β, *n*=5; mean±SD) in the thalamus at seven after the injury. **(C)** High magnification confocal images showing morphology of pericytes in cFPI + CsA Ab (upper panel, white arrow head in **A**) and cFPI + IL-1β Ab group (lower panel, white arrow in **A**). Tube-like coverage by PDGFRβ⁺ pericytes in the cFPI + IL-1β Ab group, cyan arrows. Boxed areas show cell nuclei of a pericyte stained with DAPI (grey). **(D)** Quantification of PDGFRβ⁺ pericyte coverage (sham + CsA, *n*=3; cFPI + CsA, *n*=4; sham + IL-1β, *n*=4; cFPI + IL-1β, *n*=5; mean±SD).

Neutralization of IL-1β does not affect the number of PDGFRβ expressing pericytes after diffuse TBI

We finally examined cFPI-induced changes in pericytes distribution in the cortex and thalamus of all groups using brightfield microscopy and image analyses for PDGFRβ, a marker for brain pericytes. PDGFRβ⁺ pericytes with a prominent cell body and long process were identified throughout the cortex and thalamus (Figures 5A,B), distributed in different cortical layers and thalamic regions in all groups at 2 dpi (Figure 5) and 7 dpi and (Figure 6). At 2 dpi, quantitative analysis showed a 50% decrease in the numbers of PDGFRβ⁺ pericytes in the cortex ($p=0.0005$) (Figure 5C) and thalamus ($p<0.001$) (Figure 5D) in the cFPI + CsA Ab group when compared to the sham + CsA Ab group, indicating that cFPI leads to pericyte loss. However, pericyte numbers in the cFPI + IL-1β Ab and sham + IL-1β Ab groups remained unchanged at 2 dpi.

Similarly, at 7 dpi, the number of PDGFRβ⁺ pericytes was significantly decreased in the cortex ($p=0.003$) and thalamus ($p=0.024$) in the cFPI + CsA Ab group when compared to the sham + CsA Ab group illustrating that the pericyte loss was persistent in the cFPI + CsA Ab group (Figures 6A–D). At 7 dpi, pericytes numbers were not significantly increased by neutralizing anti-IL-1β antibody treatment in any of the groups compared to the cFPI + CsA Ab group ($p=0.061$ cortex) (Figure 6C); ($p=0.155$ thalamus) (Figure 6D).

Discussion

In experimental and human TBI, the production of IL-1β increases rapidly after the injury and this may be directly involved in

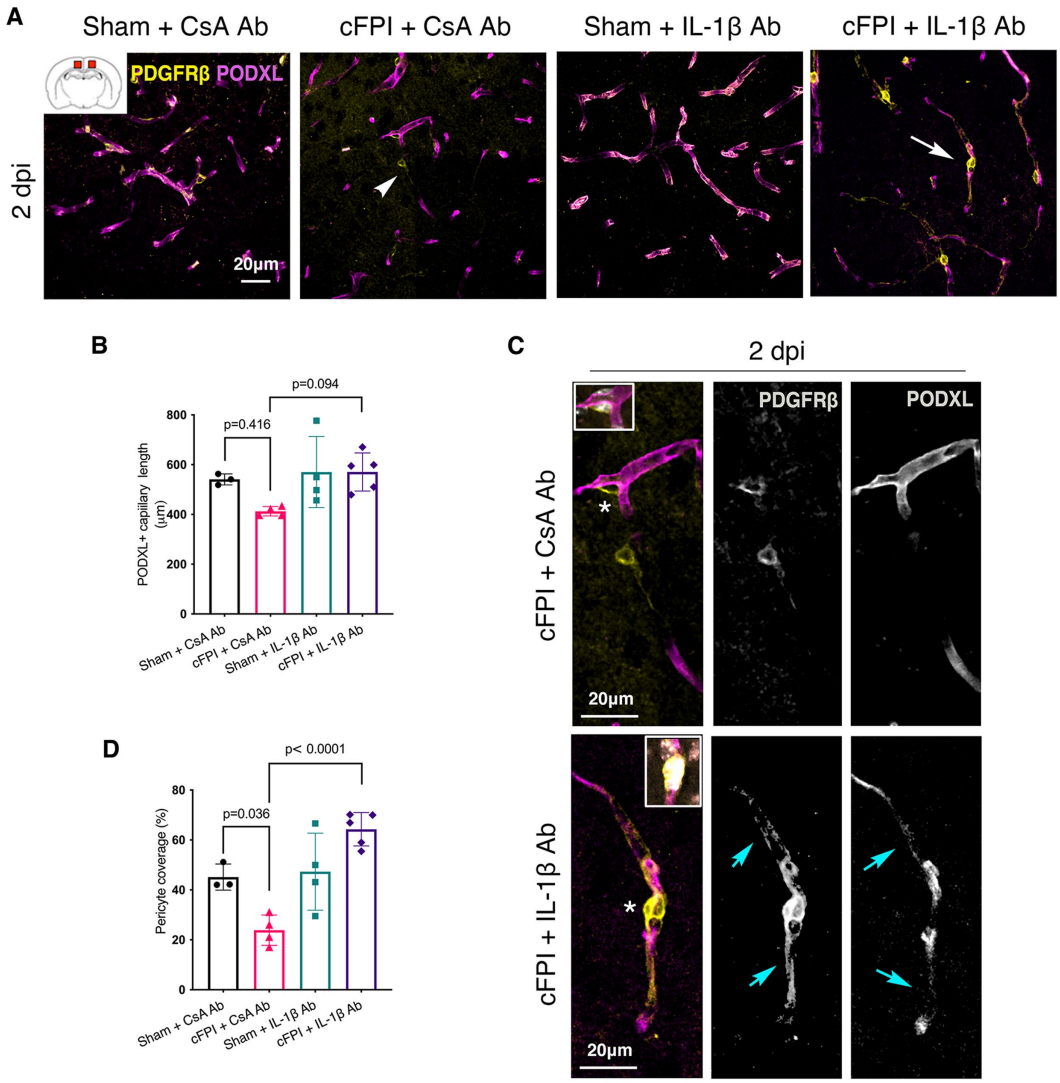

FIGURE 3
IL-1β neutralization normalizes pericyte coverage in the cortex at 2 dpi. **(A)** Representative confocal images showing podocalyxin⁺ (PODXL) capillaries (magenta) and PDGFRβ⁺ pericyte (yellow) coverage in the cortex at 2 dpi. **(B)** Quantification of total capillary length (sham + CsA Ab, $n = 3$; cFPI + CsA Ab, $n = 4$; sham + IL-1β Ab, $n = 4$; cFPI + IL-1β Ab, $n = 5$; mean ± SD) in the cortex at 2 days after the injury. **(C)** High magnification confocal images showing morphology of pericytes in cFPI + CsA Ab (upper panel, white arrow head in **A**) and cFPI + IL-1β Ab group (lower panel, white arrow in **A**). Higher coverage by PDGFRβ⁺ pericytes in cFPI + IL-1β Ab group, cyan arrows. Boxed areas show cell nuclei of a pericyte stained with DAPI (grey). **(D)** Quantification of PDGFRβ⁺ pericyte coverage (sham + CsA Ab, $n = 3$; cFPI + CsA Ab, $n = 4$; sham + IL-1β Ab, $n = 4$; cFPI + IL-1β Ab, $n = 5$; mean ± SD).

neuroinflammatory processes associated with neurodegeneration (11, 17, 37). Here, we demonstrated that IL-1β neutralization has an impact on preservation of capillaries and especially increases pericyte coverage, and those effects were more pronounced in the thalamus, a region particularly sensitive to the TBI in this model.

Diffuse axonal and diffuse vascular injuries are the most common hallmarks of TBI, where widespread lesions are commonly observed throughout white and deep grey matter structures. The cFPI model is clinically relevant experimental rodent model to examine its pathology in brain regions not directly targeted by the physical impact of the delivered fluid pressure pulse (34, 37, 39). The cFPI model results in widespread pathology, also in brain regions not directly targeted by the physical impact. The thalamus is a critical brain region relaying sensory information to the cortex. It also involves several other vital functions, such as cognition, motor control, and sleep-wake cycle regulation (40). The thalamus is particularly vulnerable to the effects of diffuse injury in the experimental TBI, and this has significant clinical implications (7, 8). For instance, long-term MRI imaging studies have revealed a reduction in cerebral flow in the thalamus of individuals with mild TBI, which was associated with cognitive impairment (21). In addition to axonal injury and inflammation, interconnected capillary network in remote areas can be at risk of disruption by mechanical forces of a diffuse brain injury. In this study, we showed that cFPI resulted in a significant decrease in total capillary length in the thalamus 2 and 7 dpi, findings consistent with previous work demonstrating that cFPI caused a significant decrease in microvascular density (25), which was reversed by neutralization of IL-1β. The reduction in vascular density during acute phases of lateral fluid percussion models in rats has been shown to correlate with functional decrements (23, 25).

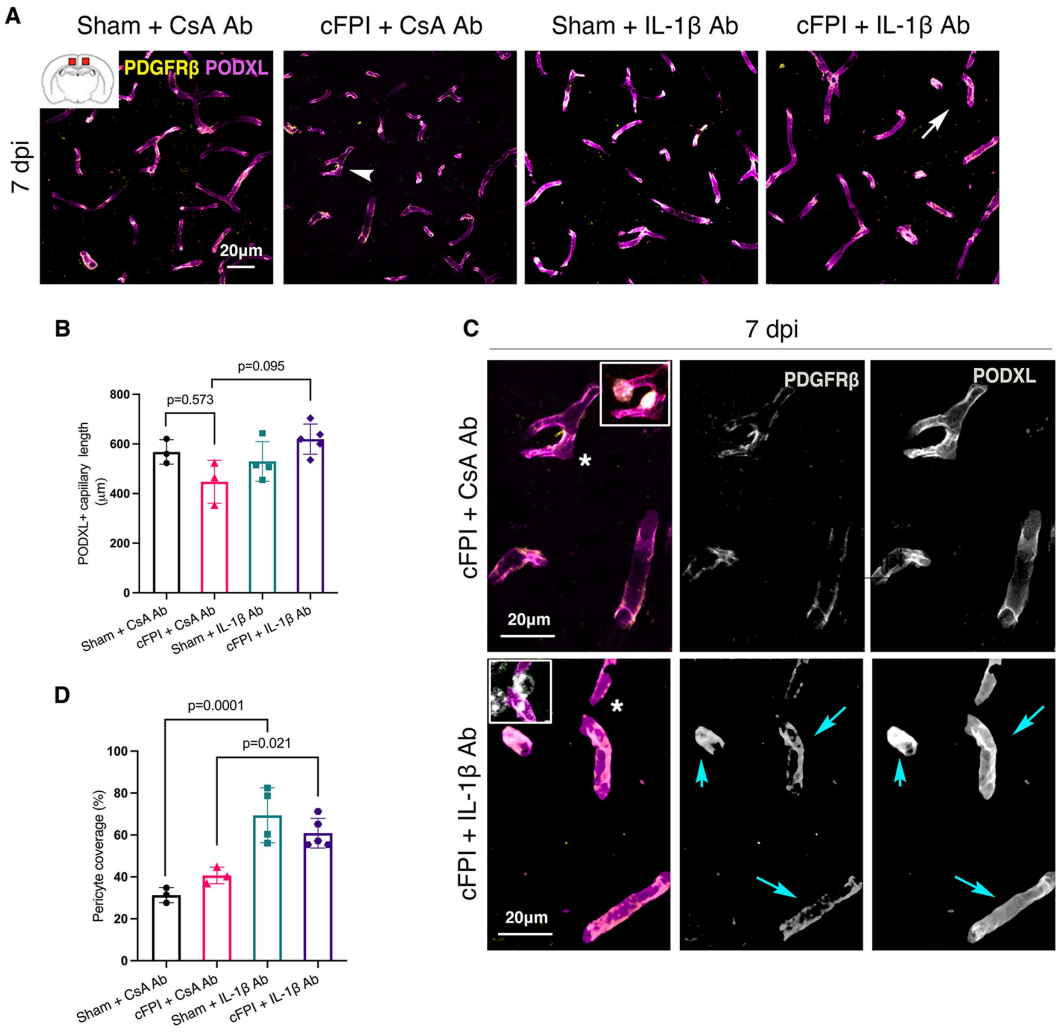

FIGURE 4
IL-1β neutralization has no significant effect on pericyte coverage and capillary length in the injured cortex at 7 dpi. Representative confocal images showing podocalyxin⁺ (PODXL) capillaries (magenta) and PDGFRβ⁺ pericyte (yellow) coverage in the cortex at 7 dpi. (**B**) Quantification of total capillary length; (sham + CsA Ab, $n = 3$; cFPI + CsA Ab, $n = 3$; sham + IL-1β Ab, $n = 4$; cFPI + IL-1β Ab, $n = 5$; mean ± SD) in the cortex at 7 days post- injury. (**C**) High magnification confocal images showing morphology of pericytes in cFPI + CsA Ab (upper panel, white arrow head in **A**) and cFPI + IL-1β Ab group (lower panel, white arrow in **A**). PDGFRβ⁺ pericytes coverage in cFPI + IL-1β Ab group, cyan arrows. Boxed areas show pericyte cell nuclei, stained with DAPI (grey). (**D**) Quantification of PDGFRβ⁺ pericyte coverage (sham + CsA Ab, $n = 3$; cFPI + CsA Ab, $n = 3$; sham + IL-1β Ab, $n = 4$; cFPI + IL-1β Ab, $n = 5$; mean ± SD).

The central fluid percussion resulted in a decreased number of PDGFRβ-expressing pericytes in the thalamus and cortex at 2 and 7 days after TBI. These findings are supported by previous studies in rodent FPI models where regional pericyte loss is observed (41). Given that pericytes are highly susceptible to brain injury and ischemia, any disruption of the crosstalk between pericyte and the vascular wall can lead to pericyte malfunction and degeneration during the subacute phase of brain injury (29, 30, 41). In the acute phase of TBI, a subgroup of pericytes migrates away from the blood vessels while the remaining ones around the endothelium undergo degeneration and display apoptotic or necrotic cellular changes (42, 43). However, the anti-IL-1β neutralizing antibody did not influence the number of pericytes at any time point arguing against a role for IL-1β in TBI-induced pericyte death in the cortex and thalamus.

The heterogeneity in the morphological pattern of pericyte processes has been described in several studies (44, 45), indicating the complexity of their structure and function. Several studies using high-resolution optical imaging have attempted to classify capillary pericytes based on their morphology in recent years. There are two main types of capillary pericytes—"thin-strand pericytes" and "mesh pericytes" (46). Thin strand pericytes display a prominent cell body and elongated processes, while mesh pericytes have higher levels of vessel coverage. These findings suggest that classifying capillary pericytes based on their morphology may provide valuable insights into their function and help understand their role in various pathological processes. It is important to note that TBI can result in increased blood-brain barrier permeability, leading to the dysfunction of cerebral autoregulation and edema formation (9, 20, 22). Therefore, our current study shows that pericyte remodeling is crucial to maintaining capillary network function following diffuse brain injury. The cFPI resulted in a rapid decrease in PDGFRβ⁺ pericyte coverage in thalamus and the cortex at 2 days post injury, however, these

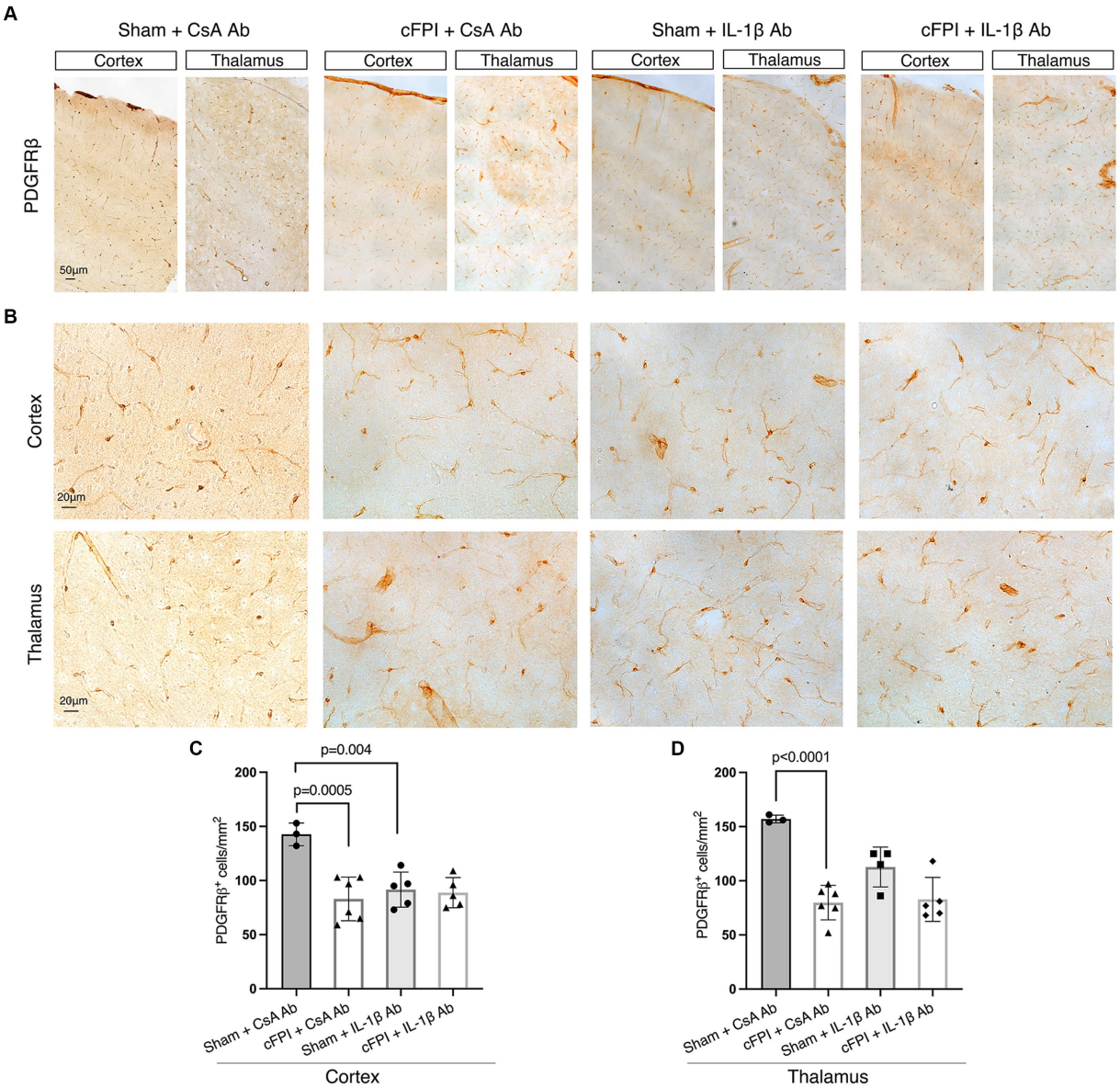

FIGURE 5
IL-1β neutralization does not influence PDGFRβ⁺ pericyte numbers in the cortex and thalamus at 2 days post-injury. **(A,B)** Representative images showing PDGFRβ staining in the cortex and thalamus at 2 dpi **(A)**, in higher magnification in **(B)**. (**C,D**) Quantification of the number of PDGFRβ⁺ pericytes in cFPI + IL-1β Ab vs. other groups (sham + CsA Ab, sham + IL-1β Ab, and cFPI + CsA Ab) in the cortex **(C)** and thalamus **(D)**. (**C**) Neutralizing IL-1β had no effect on the number of PDGFRβ⁺ pericytes in the cortex at 2 dpi (sham + CsA Ab, $n = 3$; cFPI + CsA Ab, $n = 6$; sham + IL-1β Ab, $n = 5$; cFPI + IL-1β Ab, $n = 5$). (**D**) In the thalamus, the number of PDGFRβ⁺ pericytes in the cFPI + CsA Ab animals was not influenced by IL-1β neutralizing antibody treatment (sham + CsA Ab, $n = 3$; cFPI + CsA Ab, $n = 6$; sham + IL-1β Ab, $n = 4$; cFPI + IL-1β Ab, $n = 5$; mean ± SD).

changes were no longer detectable in both regions at 7 days post injury. Regardless of structural heterogeneity, we observed that of PDGFRβ⁺ pericytes extended their process into the uncovered capillary bed in vessel areas where PODXL expression was absent at 2 dpi in both regions. This may reflect their early contribution to neovascularization and vascular remodeling after brain injury (26, 47). On the other hand, as pericytes regulate the stabilization and the function of blood vessels, it is likely that they extend their processes to preserve their endothelial contact after pericyte loss (26, 48). Most importantly, neutralizing IL-1β antibody treatment after diffuse TBI increased pericyte coverage in the thalamus 2 days after injury, which aligns with our previous findings that neutralizing IL-1β antibody reduced TBI-induced hemispheric edema at 2 dpi (20).

Chronic follow-up studies using lateral FPI model in rats show that long-lasting angiogenic response in the thalamus showed difference compared to cortical areas after the injury, which was associated with functional abnormalities (49). Although potential mechanisms underlying the mechanisms of vascular modulation require further investigation, the coinciding presence of inflammation with capillary reduction after TBI indicates that a post-injury inflammatory response may be involved in modulation of vascular response in a time/region dependent way. Here, we found that brain pericytes, highly expressing PDGFRβ, acquired more rounded morphology around the capillaries in the thalamus and cortex at 7 dpi. These pericytes with full coverage around the precapillary exhibit the highest capability of altering the cerebrovascular flow resistance,

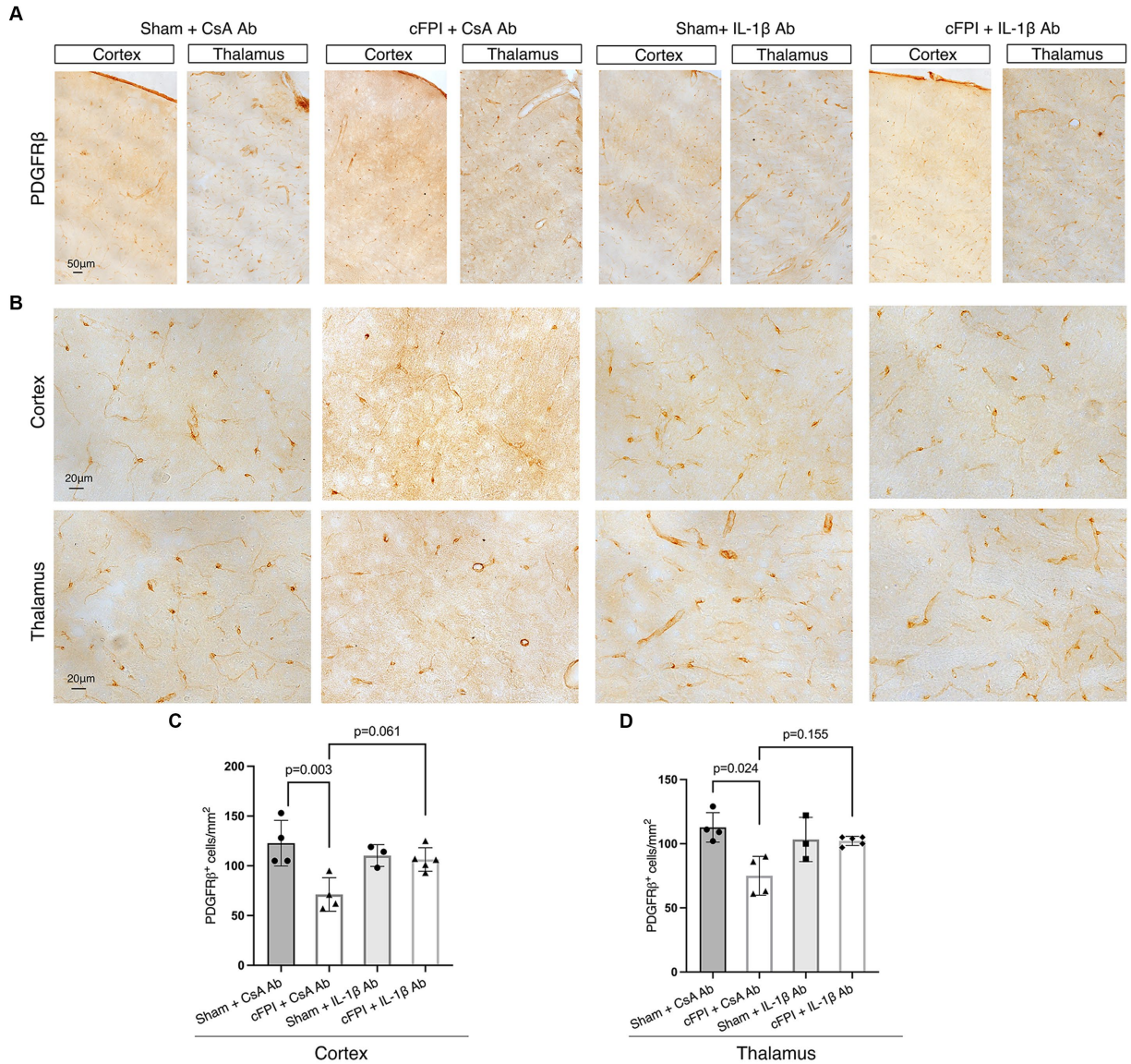

FIGURE 6
The number of PDGFRβ⁺ pericytes remains unchanged in the cortex and thalamus after IL-1β neutralization at 7 days post-injury. (**A,B**) Representative images showing PDGFRβ staining in the cortex and, thalamus at 7 dpi (**A**), higher magnification in (**B**). (**C,D**) Quantification of the number of PDGFRβ⁺ pericytes in cFPI + IL-1β Ab animals compared with other groups (sham + CsA Ab, sham + IL-1β Ab, and cFPI + CsA Ab) in the cortex **(C)** and thalamus **(D)**. (**C**) At 7 dpi, neutralizing anti-IL-1β had no effect on the number of PDGFRβ⁺ pericytes in the cortex (sham + CsA Ab, $n = 4$; cFPI + CsA Ab, $n = 4$; sham + IL-1β Ab, $n = 3$; cFPI + IL-1β Ab, $n = 5$; mean ± SD) and thalamus (sham + CsA Ab, $n = 4$; cFPI + CsA Ab, $n = 4$; sham + IL-1β Ab, $n = 3$; cFPI + IL-1β Ab, $n = 5$; mean ± SD).

particularly in the thalamus (26). Consequently, they may be responsible for regulating blood flow through the capillaries while protecting the downstream capillary bed and the thalamus from any unfavorable pressure fluctuations (18). Indeed, the thalamus is highly vascularized by arteries maintaining its normal functioning, and any disruption in their blood supply can lead to significant neurological deficits, including cognitive impairment, and motor deficits (5, 21, 50). Our previous study used the multivariate concentric square field (MCSF) and the Morris water maze (MWM) tests to assess functional outcomes post-injury. We showed that treatment with the IL-1β-neutralizing antibody, as used in the present study, attenuated stereotypic behaviors induced by TBI at 2 dpi and 9 dpi (35). However, these tests might not detect thalamic dysfunction after diffuse TBI. Advanced imaging techniques including MRI may be necessary to accurately assess changes in the blood flow and its relation to neurological functions and inflammation of the thalamus following TBI. Nevertheless, acute and chronic inflammation in the different brain regions after vascular damage may lead to behavioral changes even in the absence of detectable neuronal pathology (50). Using lateral FPI in rats, acute and persistent inflammation in the brain after vascular damage leads to neurobehavioral changes that could be reversed using immunotherapy (51). The primary effect IL-1β on endothelial cells in the brain is to increase vascular permeability and inflammation in both trauma-induced and ischemic induced lesions (52, 53); however, our findings show that neutralizing IL-1β antibody may have region-dependent diverse functions on the cerebral

vasculature. Furthermore, the administration of IL-1β neutralizing antibody increased pericyte coverage in sham-injured mice similar to injured cortex at 7 dpi, indicating that the surgical procedure used also in sham injury could trigger a minor delayed inflammatory response in the cortex.

There are several limitations of our study to consider. Although previous studies using experimental mouse models reported evidence of thalamic injury and neuronal death following TBI (54, 55), in the present study we did not analyze the possible effect of neutralizing IL-1β antibody on neuronal loss in the thalamus and cortex. However, in previous studies in mice, this treatment strategy was found to reduce the TBI-induced loss of cortical tissue indicating a potential effect on neuronal survival (20). The antibody is known to reach the mouse brain in therapeutic concentrations (>30 μg/g brain tissue) at both 24 and 72 h post-injury. Although the dosing interval for neutralizing IL-1β antibody was similar to that of previous studies (35), we did not specifically determine the endogenous levels of IL-1β in the cortex and thalamus as well as in the vascular cells after the cFPI and antibody treatment in the present study. However, the increase of IL-1β is expected to occur in the first post-injury hours (15) and at time of our study endpoints at 2 and 7 dpi, tissue IL-1β levels are presumably low (56, 57). In addition, it remains to be investigated in future studies whether neutralization of IL-1β antibody may influence blood flow regulation, capillary diameter, and BBB integrity.

Overall, our study raises awareness that the modulation of the damaged microvascular environment is an important therapeutic intervention in TBI, in which capillary regression is a factor.

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

All experiments were approved by the Uppsala County Animal Ethics board and followed the regulations of the Swedish Animal Welfare Agency. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

IÖ: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. FC: Investigation, Methodology, Writing – original draft. JF: Methodology, Writing – review & editing. NM: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. GP: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was supported by VR (Swedish Research Council): M2018-02500, Swedish Brain Foundation (2021-0421), Hans-Gabriel and Alice Trolle-Wachtmeister Foundation (HGATW; no grant number), and Alborada trust.

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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frontiers | Frontiers in Neurology

TYPE Opinion
PUBLISHED 03 May 2024
DOI 10.3389/fneur.2024.1391270

OPEN ACCESS

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RECEIVED 25 February 2024
ACCEPTED 18 April 2024
PUBLISHED 03 May 2024

CITATION
Omer GL, Maurizi R, Velletrani G, Francavilla B, Ali SS, Abdullah AS and Di Girolamo S (2024) Traumatic tension pneumocephalus: a case report and perspective from Indonesia. *Front. Neurol.* 15:1391270. doi: 10.3389/fneur.2024.1391270

Traumatic tension pneumocephalus: a case report and perspective from Indonesia

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KEYWORDS

tension pneumocephalus, endoscopic endonasal, head trauma, craniotomy, ethmoidal defect

1 Introduction

We read with great interest the recent Article by Harlyjoy et al. (1) focusing on the management of traumatic tension pneumocephalus (TP) and the associated challenges in treating patients with head trauma in low- and middle-income countries (LMICs) (1). The authors' exploration into optimizing treatment protocols to reduce hospitalization times and minimize post-operative complications is both timely and pertinent. They notably underscore the critical need to address delays in the management of traumatic brain injuries by enhancing the utilization of health resources. We would like to provide our insights based on our experience in managing TP caused by post-traumatic ethmoidal damage, further contributing to this essential dialogue.

2 Discussion

While Pneumocephalus is a condition characterized by the presence of air in the intra cranial space caused by a breach in the cranium dural barrier, in TP air is progressively accumulated in the intra cranial space by a "ball valve" or "inverted pop bottle" mechanism. This mechanism categorizes TP as emergency condition due to the compressive effect of the trapped air on the brain. In the management of TP, the primary objective is the emergent decompression to alleviate intracranial pressure, combined with the repair of the causative defect (2). Endoscopic multilayer repair is the standard treatment for closing the craniodural breach. To achieve adequate intracranial decompression, the historical craniectomy has been replaced with the more recent craniotomy (3). Despite its efficacy, craniotomy is associated with a notable risk profile including soft tissue infection, extradural abscesses, subdural empyema, bone flap infection, and postoperative intracranial infection (4). Shi et al. (5) reported their experience with post craniotomy intracranial infection (PCII), showing a PCII rate of 6.8% among 5,732 patients.

Recent studies have explored various endoscopic techniques that simultaneously address the resolution of traumatic tension pneumocephalus (TP) and the closure of the bone defect responsible for cerebrospinal fluid leakage in a single surgical stage (6, 7). The development of new techniques and more angulated instruments for endoscopic surgery has increased the possibility of accessing more challenging endonasal areas (8). Single-step endonasal procedures may effectively treat both the TP and the craniodural defect

concurrently, significantly lowering the risks of complications and shortening the duration of hospital stays. Patients treated with these strategies can expect reduced postoperative morbidity, quicker discharge, and a faster return to work. This is particularly relevant in LMICs, where the healthcare infrastructure may not support extensive postoperative care, and where the economic impact of prolonged hospitalization can be substantial.

To the best of our knowledge, the literature offers only four examples of TP resulting from post-traumatic ethmoidal roof damage, complicating the development of precise management guidelines. However, with equal effectiveness, the more appropriate direction should focus on procedures that allow a reduction in post-operative hospital stays and complications rate.

In conclusion, the adoption of endonasal endoscopic approaches for the first-line treatment of symptomatic TP due to post-traumatic ethmoidal defects offers a promising opportunity to improve patient outcomes not just in LMICs, but globally. This method underscores the potential of minimally invasive surgical techniques in TP management, promoting a model that prioritizes efficiency, safety, and accessibility while addressing the challenges of limited healthcare infrastructure and resources.

Author contributions

GLO: Writing – review & editing. RM: Writing – original draft, Writing – review & editing. GV: Writing – review & editing. BF: Writing – review & editing. SSA: Writing – review & editing. ASA: Writing – review & editing. SD: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 24 May 2024
DOI 10.3389/fpubh.2024.1349169

OPEN ACCESS

EDITED BY
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RECEIVED 08 December 2023
ACCEPTED 13 May 2024
PUBLISHED 24 May 2024

CITATION
He J, Chen Z, Zhang J and Liu X (2024) Knowledge and attitudes toward mild traumatic brain injury among patients and family members.
Front. Public Health 12:1349169.
doi: 10.3389/fpubh.2024.1349169

Knowledge and attitudes toward mild traumatic brain injury among patients and family members

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Introduction: Mild traumatic brain injury (mTBI) is a prevalent health issue with significant effects on patients' lives. Understanding and attitudes toward mTBI among patients and their families can influence management and outcomes. This study aimed to assess knowledge and attitudes toward mTBI in these groups.

Methods: A cross-sectional study was conducted at Zhejiang Hospital from July 1, 2023, to September 30, 2023. Patients with mTBI and their family members participated. Data were collected via an online questionnaire covering demographic information and mTBI knowledge and attitudes. Knowledge scores ranged from 0 to 20 and attitude scores from 8 to 40. Multivariate logistic regression identified factors influencing these scores.

Results: A total of 573 valid questionnaires were analyzed (289 males, 50.44%; 284 females, 49.56%). Among respondents, 258 (45.03%) had experienced a concussion. Mean knowledge and attitude scores were 11.00 ± 2.75 and 27.78 ± 4.07, respectively. Monthly per capita income of 5,000–10,000 RMB was negatively associated with knowledge and attitude scores ($\beta = 0.160$, 95% CI: [3.245 to 0.210], $P = 0.026$). Middle school education decreased the likelihood of positive attitudes toward mTBI (OR = 0.378, 95% CI: [0.1630.874], $P = 0.023$). mTBI due to falls was associated with increased likelihood of positive attitudes (OR = 3.588, 95% CI: [1.274–10.111], $P = 0.016$).

Discussion: Significant gaps in knowledge and attitudes toward mTBI exist among patients and their families, influenced by income and education levels. Personal experience with mTBI from falls correlates with more positive attitudes. These findings highlight the need for targeted educational interventions to improve understanding and attitudes, ultimately enhancing patient care and management. Comprehensive, accessible mTBI education is crucial for fostering positive attitudes and better knowledge among patients and their families.

KEYWORDS

knowledge, attitude, traumatic brain injury, patients, cross-sectional study

1 Background

Traumatic brain injury (TBI) encompasses a spectrum of severity, with mild traumatic brain injury (mTBI) or concussion being the most common subtype, constituting over 80% of TBI cases (1–3). The disruption of extensive brain networks by TBI, particularly in cases of mTBI, underscores the significant neurological effects even seemingly minor physiological disturbances can induce (4, 5). The clinical significance and long-term implications of mTBI are profound, with affected individuals potentially experiencing a wide array of consequences, including but not limited to headaches, dizziness, neck pain, drowsiness, issues with balance and vision, memory impairment, emotional and mood disturbances, fatigue, and sleep disruptions (6). As a significant global health concern, TBI is associated with elevated mortality rates, disability, and reduced health-related quality of

life (7). This condition poses a serious threat to individuals' lives and has a profound effect on their overall wellbeing. Annually, over 27 million people worldwide experience TBI (8), frequently resulting in cognitive and functional deficits, impeding daily life activities, and diminishing overall quality of life (9–11). Therefore, a comprehensive approach is essential to address TBI, with a specific focus on mTBI, as it is a common contributor to neurological morbidity and a leading cause of disability, adversely affecting patient function and quality of life.

In accordance with the Knowledge, Attitude, and Practice (KAP) model, individual behaviors are influenced by their knowledge and attitude (12). Knowledge can be considered as a distal determinant of behavior, which is mediated by attitude. Knowledge holds particular significance in shaping attitudes toward health-related behaviors within the framework of the knowledge-attitude-behavior model (13). Given that patients and their family members are either directly affected by or closely connected to individuals with mTBI, their levels of knowledge and attitudes assume a pivotal role in the processes of rehabilitation and management. Gaining insights into their perspectives and needs can greatly aid healthcare professionals in better fulfilling their requirements and delivering more effective medical care. Currently, there is a notable absence of pertinent research within this specific domain, underscoring an existing gap in the academic literature.

Therefore, this study aimed to investigate the knowledge and attitudes toward mTBI among patients and their family members.

2 Methods

2.1 Study design and participants

This cross-sectional study was conducted between July 1, 2023 and September 30, 2023 at Zhejiang Hospital among patients and their family members of mTBI. This study received ethical approval from the Medical Ethics Committee of Zhejiang Hospital and obtained informed consent from all participants. Inclusion Criteria: (1) Patients with mild traumatic brain injury/Family members of patients with mild traumatic brain injury; (2) History of mild traumatic brain injury within the past year. Mild TBI (mTBI) is defined as the initial Glasgow coma score (GCS) of 13–15, loss of consciousness (LOC) of <30 min, duration of change in mental state (AOC), and posttraumatic amnesia (PTA) of <24 h after external violence on the patient's head, with a negative head CT scan result (14). Exclusion criteria included: (1) Questionnaire completion time of <90 s, suggesting insufficient engagement; (2) Participants expressing disagreement in their responses, indicating potential misunderstandings; (3) Incorrect answers to trap questions designed to test the accuracy of knowledge. Informed consent was obtained from all participants.

2.2 Questionnaire and quality control

The questionnaire was developed based on the 2022 Neurosurgery Guidelines for Diagnosis and Treatment of Cranial Injuries and previous literatures (15–17). A pilot test was conducted involving a small sample of 22 respondents. Participants were recruited through a randomized questionnaire survey administered by neurosurgeons, targeting patients with mild brain injuries and their families at neurosurgery outpatient and inpatient clinics. The internal consistency of the questionnaire was assessed using Cronbach's α coefficient, which yielded a value of 0.856, indicating satisfactory internal reliability. The final questionnaire comprised four sections: demographic information (covering gender, age, education, and professional title), a knowledge section, and an attitude section. The knowledge segment encompassed 13 questions, with the 9th and 10th questions each containing 6 and 3 sub-questions, respectively. Respondents received 1 point for correct answers and 0 points for incorrect or unclear responses, resulting in a knowledge score range of 0–20 points. The attitude section consisted of eight questions, employing a five-point Likert scale ranging from very positive (five points) to very negative (one point), with a total score range of 8–40 points. Positive attitude was defined as achieving scores surpassing 70% of the maximum possible score in each respective section (18–20).

Online e-questionnaires were created using the Wen-Juan-Xing online platform in China (https://www.wjx.cn/app/survey.aspx), and QR codes were provided for access to the electronic version. The distribution of questionnaires occurred in emergency surgery, neurosurgery, and orthopedic consultation rooms, as well as during follow-up visits and appointments with patients recovering from cerebral concussion, facilitated by psychiatrists and orthopedic doctors. To ensure the quality and completeness of the questionnaire results, each IP address could only be used once for submission, and every question was mandatory. The research team meticulously checked all questionnaires for completeness, consistency, and validity.

2.3 Statistical analysis

Data analysis was conducted using SPSS 26.0 (IBM, Armonk, NY, USA). Continuous data are presented as means and standard deviations (SD), while categorical data are expressed as n (%). Continuous variables underwent a normality test, with the t-test for normally distributed data and the Wilcoxon Mann–Whitney test for non-normally distributed data when comparing two groups. For three or more groups with normally distributed continuous variables and uniform variance, ANOVA was used for comparisons, while the Kruskal–Wallis test was employed for non-normally distributed data. Multivariate analysis was used to explore the factors influencing knowledge and attitudes score and positive attitudes. A two-sided P-value < 0.05 was considered statistically significant.

3 Results

Initially, a total of 950 questionnaires were collected in the study, excluding 12 cases of questionnaires with too short response time (<90 s); two cases of disagreement with participation; and 363 cases of wrong answers to the trap questions of the knowledge dimensions, leaving 573 valid questionnaires with an effective rate of 60.25%. One of the questionnaires was not filled in for age, which was supplemented by using the mean value. Among them,

TABLE 1 Baseline characteristics and KA scores.

	N (%)	Knowledge, mean ± SD	*P*-value	Attitude, mean ± SD	*P*-value
N = 573					
Total score		11.00 ± 2.75		27.78 ± 4.07	
Gender			0.988		0.607
Male	289 (50.44)	11.00 ± 2.48		27.87 ± 3.74	
Female	284 (49.56)	11.00 ± 2.99		27.69 ± 4.38	
Age, years			0.656		<0.001
18–40	312 (54.45)	10.93 ± 2.94		28.23 ± 4.08	
41–59	257 (44.85)	11.10 ± 2.38		27.15 ± 3.93	
60 and above	4 (0.70)	10.25 ± 7.14		33.25 ± 4.50	
Residence			0.151		0.585
Rural	93 (16.23)	10.62 ± 2.90		27.99 ± 4.23	
Urban	480 (83.77)	11.07 ± 2.71		27.74 ± 4.04	
Education			0.136		0.007
Primary school and below	58 (10.12)	11.45 ± 2.13		27.43 ± 3.73	
Middle school	159 (27.75)	11.04 ± 2.44		27.18 ± 3.74	
High school/technical secondary school	72 (12.57)	11.17 ± 2.77		27.04 ± 3.74	
Junior college/undergraduate	203 (35.43)	10.63 ± 3.18		28.58 ± 4.30	
Postgraduate and above	81 (14.14)	11.37 ± 2.42		27.85 ± 4.36	
Medical-related occupation			0.071		0.100
Yes	2 (0.35)	14.50 ± 2.12		32.50 ± 2.12	
No	571 (99.65)	10.99 ± 2.74		27.76 ± 4.07	
Monthly per capita income, RMB			0.029		0.063
<2,000	56 (9.77)	11.36 ± 2.13		27.89 ± 3.27	
2,000–5,000	168 (29.32)	11.27 ± 2.50		27.35 ± 3.45	
5,000–10,000	173 (30.19)	10.47 ± 3.07		27.42 ± 4.33	
10,000–20,000	120 (20.94)	10.99 ± 2.57		28.43 ± 4.22	
>20,000	56 (9.77)	11.48 ± 3.09		28.66 ± 5.04	
Marital status			0.554		0.893
Unmarried	94 (16.40)	10.72 ± 2.87		27.84 ± 3.76	
Married	322 (56.20)	11.11 ± 2.83		27.86 ± 4.54	
Divorced	106 (18.50)	10.82 ± 2.45		27.63 ± 3.30	
Widowed	51 (8.90)	11.14 ± 2.57		27.45 ± 2.77	
Reason of mTBI			0.007		<0.001
Sports	148 (25.83)	11.01 ± 2.42		27.64 ± 4.04	
External collisions, such as a car accident	218 (38.05)	11.29 ± 2.51		27.53 ± 3.78	
Falling from a height or other	21 (3.66)	9.19 ± 5.01		31.43 ± 5.51	
Accidental falls	186 (32.46)	10.85 ± 2.84		27.77 ± 4.07	
Times of concussion experienced by you (or patients in your household)			0.365		0.278
Once	258 (45.03)	11.03 ± 2.59		27.93 ± 3.86	
Twice	140 (24.43)	11.10 ± 2.77		27.69 ± 3.65	
3 or more	84 (14.66)	11.21 ± 2.43		27.06 ± 4.28	
Unclear	91 (15.88)	10.55 ± 3.34		28.16 ± 4.95	

TABLE 2 Responses in the knowledge dimensions.

Items, *n* (%)	Correctness rate
1. Concussion is also known as mTBI	475 (82.90)
2. Altered consciousness in concussion includes conditions such as mental confusion, amnesia, or loss of consciousness	325 (56.72)
3. After head trauma, a brief period of unconsciousness may occur immediately, with consciousness often returning within 30 min	336 (58.64)
4. Concussion can potentially result in brain injury even if a person does not lose consciousness	332 (57.94)
5. It is necessary for concussion patients to experience a loss of consciousness	388 (67.71)
6. Individuals who have suffered a concussion may have difficulty recalling events that occurred before the concussion	320 (55.85)
7. MTBI is more severe than a concussion	475 (82.90)
8. The use of cranial computed tomography scans or magnetic resonance imaging can determine if brain injury has occurred due to a concussion	318 (55.50)
9. **Characteristics of concussion include:**	
9.1. Purposeless staring or unclear speech	348 (60.73)
9.2. Delayed language and motor responses	351 (61.26)
9.3. Easily distracted attention and an inability to concentrate	324 (56.54)
9.4. Difficulty discerning date, time, and location	266 (46.42)
9.5. Motor incoordination: stumbling while walking	328 (57.24)
9.6. Memory impairment: repeating the same question	289 (50.44)
10. **Common psychological symptoms in concussion patients include:**	
10.1. Irritability or easy anger	309 (53.93)
10.2. Sadness or depression	335 (58.46)
10.3. Nightmares	97 (16.93)
11. Patients with concussion typically do not require specialized treatment	113 (19.72)
12. Individuals who have not yet recovered from a concussion should avoid further head impacts	407 (71.03)
13. One of the methods for assessing the recovery progress after a concussion is to inquire about the patient's feelings	166 (28.97)

289 (50.44%) were males, 312 (54.45%) were aged 18–40 years, 203 (35.43%) had junior college or undergraduate education. Two hundred-eighteen (38.05%) suffered from mTBI due to external collision such as a car accident, and 258 (45.03%) experienced once of concussion.

The mean knowledge and attitude scores were 11.00 ± 2.75 (possible range: 0–20) and 27.78 ± 4.07 (possible range: 8–40), respectively. The knowledge score varied from patients with different monthly per capita income ($P = 0.029$) and the reasons they suffered a mTBI ($P = 0.007$). As for the attitude score, there were difference among patients with different age ($P < 0.001$), education ($P = 0.007$), and the reasons they suffered a mTBI ($P < 0.001$; Table 1).

The distribution of knowledge dimensions revealed that the three knowledge items with the highest correctness rates were as follows: "*Concussion is also known as mTBI.*" (K1) with 82.90%, "*mTBI is more severe than a concussion.*" (K7) with 82.90%, and "*Individuals who have not yet recovered from a concussion should avoid further head impacts.*" (K12) with 71.03%. Contrarily, the three items with the lowest correctness rates were "*Common psychological symptoms in concussion patients include nightmares.*" (K10.3) with 16.93%, "*Patients with concussion typically do not require specialized treatment.*" (K11) with 19.72%, and "*One of the methods for assessing the recovery progress after a concussion is to inquire about the patient's feelings.*" (K13) with 28.97% (Table 2).

Participants' attitudes toward mTBI (concussion) varied considerably, 68.76% of respondents recognized the necessity of seeking immediate medical consultation when symptoms of a concussion are present (A1). Additionally, 67.36% stressed the importance of closely monitoring the condition following a concussion to prevent deterioration (A2). 66.97% believed that even in the absence of apparent symptoms after an external head collision, it is essential to rule out the possibility of a concussion (A3). Moreover, 65.45% acknowledged the importance of monitoring memory, either for themselves or patients in their household, following a concussion diagnosis (A4). When it came to concerns about concussion recovery (A5), 67.89% expressed varying degrees of concern, while 9.95% believed in generally good recovery and considered excessive worry unnecessary. Regarding emotional changes and attention, 68.24% agreed on the need to promptly address emotional changes for oneself or patients (A6). Conversely, only 10.65% believed that short-term memory loss symptoms following a concussion are normal, while 60.74% expressed some level of concern (A7). Furthermore, 65.79% recognized that severe symptoms resulting from a concussion could lead to consequences such as death (A8; Table 3).

TABLE 3 Responses in the attitude dimensions.

Items, *n* (%)	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
1. Immediate medical consultation is necessary when symptoms of concussion are present	261 (45.55)	133 (23.21)	138 (24.08)	21 (3.66)	20 (3.49)
2. Close observation of the condition following a concussion is necessary to prevent deterioration	177 (30.89)	209 (36.47)	133 (23.21)	24 (4.19)	30 (5.24)
3. Even without apparent symptoms after an external head collision, the possibility of a concussion should be ruled out	229 (39.97)	149 (26.00)	159 (27.75)	16 (2.79)	20 (3.49)
4. Following a concussion diagnosis, it is important to monitor memory for yourself or patients in your household	159 (27.75)	216 (37.70)	146 (25.48)	26 (4.54)	26 (4.54)
5. Recovery from a concussion is generally good, and excessive worry is unnecessary	29 (5.06)	28 (4.89)	127 (22.16)	144 (25.13)	245 (42.76)
6. Prompt attention to emotional changes for yourself or patients is necessary	246 (42.93)	145 (25.31)	139 (24.26)	22 (3.84)	21 (3.66)
7. Short-term memory loss symptoms following a concussion are normal, and excessive worry is unnecessary	35 (6.11)	26 (4.54)	164 (28.62)	234 (40.84)	114 (19.90)
8. Severe symptoms in a concussion can lead to consequences such as death	135 (23.56)	242 (42.23)	140 (24.43)	26 (4.54)	30 (5.24)

Multivariate analysis showed that monthly per capita income between 5,000 and 10,000 RMB was independently associated with knowledge and attitude score [$\beta = -0.160$, 95% CI: (-3.245 to 0.210), $P = 0.026$; Table 4]. Moreover, middle school education [OR = 0.378 95% CI: (0.163–0.874), $P = 0.023$] and suffering a mTBI due to falling from a height or other [OR = 3.588, 95% CI: (1.274–10.111), $P = 0.016$] were independently associated with positive attitude (Table 5).

4 Discussion

As evidenced by our findings, patients and family members exhibit inadequate knowledge and suboptimal attitudes toward mTBI, underscoring the critical need for healthcare professionals across various settings—from emergency surgery units to outpatient psychiatric clinics—to enhance clinical practices. This enhancement should particularly focus on patient and carer education, adapted to the specific contexts of different healthcare environments. Given the varied causes of mTBI, from sports-related concussion (SRC) to falls from a height, our study advocates for personalized support that addresses the unique challenges and needs associated with each type of injury. This approach is grounded in emerging research that supports tailored interventions based on the underlying cause of mTBI to improve patient outcomes. Beyond merely listing examples, our findings illuminate the profound implications of enhancing mTBI awareness and management. Specifically, by addressing the knowledge and attitude gaps identified, healthcare practices can evolve to more effectively educate patients and their families—especially those from lower-income backgrounds—about mTBI. Such informed engagement is crucial for improving mTBI outcomes and patient adherence to recommended care plans, thereby facilitating more effective management of mTBI.

The study findings indicate that patients and their family members exhibit inadequate knowledge and less favorable attitudes toward mTBI. These results are in line with previous studies, which has consistently highlighted a general lack of awareness and suboptimal attitudes toward TBI in healthcare settings (21, 22). The study also identifies several influencing factors, such as income, education, and the causes of TBI, which should be considered in clinical practice. For instance, socioeconomic status, as indicated by monthly per capita income, plays a significant role in knowledge and attitude scores, suggesting that tailored interventions may be necessary for individuals with lower incomes, echoing findings from studies in other health domains (23). Furthermore, education level demonstrated a significant association with attitudes toward mTBI, where individuals with higher educational backgrounds, particularly those with junior college/undergraduate degrees, exhibited more positive attitudes. This finding underscore that education not only enhances knowledge but also positively influences health-related attitudes, potentially leading to more effective coping strategies and adherence to treatment protocols in the face of health challenges. The reasons behind TBI occurrences, such as falls from heights, are associated with more positive attitudes, emphasizing the need for personalized support based on the circumstances of the injury. Additionally, variations in attitude scores among patients of different age groups and educational backgrounds highlight the importance of targeted educational initiatives. In light of these findings, healthcare professionals should prioritize patient and family education, particularly for those from diverse demographic backgrounds, to enhance clinical management and outcomes related to mTBI (24, 25).

The findings from the knowledge dimension of this study provide insight into the existing deficiencies in understanding mTBI and concussion among patients and their family members. While some respondents exhibited a relatively accurate understanding of certain aspects, such as the definition of concussion and its potential consequences, a significant proportion displayed gaps in knowledge. For instance, misconceptions regarding the necessity of experiencing loss of consciousness or the severity of mTBI compared to a concussion were prevalent.

TABLE 4 Analysis of factors affecting KA scores.

Variables	Univariate analysis		Multivariate analysis	
	β (95%CI)	*P*-value	β (95% CI)	*P*-value
Gender				
Male	0.018 (−0.635 to 0.992)	0.667		
Age				
18–40	−0.437 (−9.217 to 0.525)	0.080	−0.313 (−8.264 to 2.044)	0.236
41–59	−0.528 (−10.132 to −0.378)	0.035	−0.454 (−9.794 to 0.757)	0.093
Residence				
Rural	−0.015 (−1.299 to 0.908)	0.728		
Education				
Middle school	−0.060 (−2.151 to 0.833)	0.386		
High school/technical secondary school	−0.045 (−2.387 to 1.045)	0.443		
Junior college/undergraduate	0.032 (−1.120 to 1.775)	0.657		
Postgraduate and above	0.024 (−1.330 to 2.016)	0.687		
Medical-related occupation				
Yes	0.098 (1.384 to 15.120)	0.019	0.066 (−1.766 to 12.840)	0.137
Monthly per capita income				
<2,000	−0.054 (−2.719 to 0.933)	0.337	0.036 (−1.546 to 2.736)	0.585
2,000–5,000	−0.140 (−3.015 to −0.033)	0.045	−0.019 (−2.008 to 1.585)	0.817
5,000–10,000	−0.209 (−3.738 to −0.767)	0.003	−0.160 (−3.245 to −0.210)	0.026
10,000–20,000	−0.060 (−2.290 to 0.837)	0.362	−0.047 (−2.132 to 0.981)	0.468
Marital status				
Married	0.041 (−0.732 to 1.554)	0.480		
Divorced	−0.009 (−1.492 to 1.270)	0.875		
Widowed	0.001 (−1.671 to 1.720)	0.977		
Reason of mTBI				
External collisions, such as a car accident	0.016 (−0.875 to 1.198)	0.760		
Falling from a height or other	0.075 (−0.306 to 4.233)	0.090		
Accidental falls	−0.004 (−1.109 to 1.035)	0.946		
Times of concussion experienced by you (or patients in your household)				
Twice	−0.015 (−1.195 to 0.852)	0.742		
3 or more	−0.049 (−1.908 to 0.541)	0.273		
Unclear	−0.018 (−1.432 to 0.946)	0.688		

The reference categories for each variable are as follows: Gender (female), Age (60 and above), Residence (urban), Education (primary school and below), Medical-related occupation (no), Monthly per capita income (>20,000), Marital status (unmarried), reason of mTBI (sports), Times of concussion experienced (once).

The assessment of recovery progress after a concussion was also found to be poorly understood, as a relatively low percentage of respondents recognized the importance of assessing patients' feelings. Such knowledge gaps underline the critical need for targeted education and awareness campaigns. To improve clinical practice, initiatives should focus on disseminating accurate information about the nature of mTBI, the importance of assessing recovery, and the potential psychological symptoms (26, 27). Additionally, promoting the understanding that individuals with concussion should avoid further head impacts and that specialized treatment might be necessary for some patients is essential for enhancing the management and outcomes of mTBI cases (28, 29). For clinicians in emergency settings, this might mean emphasizing the seriousness of any head injury, regardless of immediate symptoms. In contrast, those in rehabilitation or psychiatric settings might focus on educating patients about the recovery timeline and potential psychological symptoms.

The results from the attitude dimension of this study reveal a spectrum of attitudes held by patients and their family members toward mTBI and concussion. While a notable

TABLE 5 Analysis of factors affecting positive attitudes.

Variables	Univariate		Multivariate	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Knowledge score	0.989 (0.918–1.065)	0.767		
Gender				
Male	1.044 (0.694–1.572)	0.835		
Age				
18–40	0.109 (0.011–1.065)	0.057	0.123 (0.010–1.512)	0.102
41–59	0.053 (0.005–0.520)	0.012	0.111 (0.009–1.405)	0.090
Residence				
Rural	1.487 (0.886–2.495)	0.133		
Education				
Middle school	0.387 (0.173–0.866)	0.021	0.378 (0.163–0.874)	0.023
High school/technical secondary school	0.433 (0.166–1.130)	0.087	0.514 (0.170–1.561)	0.240
Junior college/undergraduate	1.351 (0.679–2.691)	0.392	0.983 (0.233–4.143)	0.982
Postgraduate and above	1.212 (0.549–2.676)	0.635	0.888 (0.192–4.109)	0.879
Medical-related occupation				
Yes	/	0.999		
Monthly per capita income				
<2,000	0.561 (0.235–1.340)	0.193	1.189 (0.310–4.552)	0.801
2,000–5,000	0.310 (0.148–0.648)	0.002	0.624 (0.187–2.084)	0.444
5,000–10,000	0.501 (0.251–0.998)	0.049	0.610 (0.287–1.294)	0.198
10,000–20,000	0.983 (0.493–1.961)	0.962	1.058 (0.516–2.170)	0.878
Marital status				
Married	0.811 (0.472–1.394)	0.449		
Divorced	0.631 (0.316–1.261)	0.193		
Widowed	0.491 (0.195–1.240)	0.132		
Reason of mTBI				
External collisions, such as a car accident	0.911 (0.539–1.541)	0.728	1.063 (0.617–1.832)	0.826
Falling from a height or other	4.327 (1.681–11.137)	0.002	3.588 (1.274–10.111)	0.016
Accidental falls	0.848 (0.490–1.470)	0.558	0.918 (0.520–1.622)	0.768
Times of concussion experienced by you (or patients in your household)				
Twice	0.688 (0.399–1.186)	0.178		
3 or more	0.802 (0.426–1.511)	0.495		
Unclear	1.248 (0.714–2.183)	0.436		

The reference categories for each variable are as follows: Gender (female), Age (60 and above), Residence (urban), Education (primary school and below), Medical-related occupation (no), Monthly per capita income (>20,000), Marital status (unmarried), Reason of mTBI (sports), Times of concussion experienced (once).

proportion of respondents demonstrated a positive attitude by recognizing the importance of immediate medical consultation when TBI symptoms are present, and the need for close observation following a concussion, there were also prevalent neutral and negative attitudes in certain aspects. Notably, a substantial number of respondents held neutral or negative attitudes regarding the necessity of excessive worry and emotional changes following a concussion, and the potential severity of symptoms, including the possibility of death. These findings are consistent with previous studies indicating variations in attitudes toward TBI and the associated emotional and cognitive aspects (30). To address these deficiencies in attitudes, initiatives to improve clinical practice should aim at fostering a more informed and empathetic perspective. Education and counseling should be directed toward emphasizing the importance of timely medical attention, vigilant observation, and supportive

emotional care following a concussion (31, 32). Initiatives should also work to dispel misconceptions regarding symptom severity and emphasize the potential consequences of severe TBI (33, 34). Ultimately, by addressing the specific knowledge gaps and misconceptions identified in our study, these efforts are expected to foster a more positive and well-informed attitude among patients and their families. This direct targeting of educational content, informed by our findings, is anticipated to lead to better clinical management and outcomes for mTBI cases (35, 36).

This study has several limitations. First, data were collected through online questionnaires, which may introduce selection bias, as it excludes individuals without internet access or those who choose not to participate. Second, the study relies on self-reported information, which can be subject to recall bias and social desirability bias, potentially affecting the accuracy of the responses. Additionally, the study's cross-sectional design limits the ability to establish causality or assess changes in knowledge and attitudes over time. Furthermore, the study was conducted in a specific geographic area, which may limit the generalizability of the findings to other regions or populations with different socio-cultural backgrounds. The recruitment strategy utilized in this study, spanning diverse healthcare settings and periods, enriches the applicability of our findings. However, it also introduces considerations for future research, particularly in examining how seasonal variations and different healthcare environments may impact the prevalence and understanding of mTBI. Such insights could inform more nuanced approaches to patient education and care, potentially tailoring strategies to specific times of the year or patient populations.

In conclusion, patients and family members had inadequate knowledge and suboptimal attitude toward mTBI. Special attention should be given to individuals with lower monthly per capita incomes, as they exhibited less knowledge and less favorable attitudes. Tailored interventions and support programs should be developed to address the specific needs of this demographic. Additionally, recognizing the influence of injury causes on attitudes, such as falling from a height, can guide clinicians in providing personalized counseling and support.

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 Ethics Review Committee of Zhejiang Hospital [2022-139K]. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JH: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. ZC: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. JZ: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. XL: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Exploration and Prognostic Analysis of Enhanced 3D Volume Liquid Attenuation Inversion Recovery (3D-T2-FLAIR+C) Sequence in Mild Traumatic Brain Injury (2022KY474).

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/fpubh.2024.1349169/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 12 June 2024
DOI 10.3389/fneur.2024.1397625

OPEN ACCESS

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RECEIVED 07 March 2024
ACCEPTED 29 April 2024
PUBLISHED 12 June 2024

CITATION
Semework M, Laeke T, Aklilu AT, Tadele A, Ashagre Y, Teklewold P, Kolias AG, Hutchinson P, Balcha A, Yohannes D and Hassen GW (2024) Extended tests for evaluating post-traumatic brain injury deficits in resource-limited settings: methods and pilot study data.
Front. Neurol. 15:1397625.
doi: 10.3389/fneur.2024.1397625

Extended tests for evaluating post-traumatic brain injury deficits in resource-limited settings: methods and pilot study data

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Introduction: Traumatic brain injury (TBI) is one of the leading causes of all injury-related deaths and disabilities in the world, especially in low to middle-income countries (LMICs) which also suffer from lower levels of funding for all levels of the health care system for patients suffering from TBI. These patients do not generally get comprehensive diagnostic workup, monitoring, or treatment, and return to work too quickly, often with undiagnosed post-traumatic deficits which in turn can lead to subsequent incidents of physical harm.

Methods: Here, we share methods and results from our research project to establish innovative, simple, and scientifically based practices that dramatically leverage technology and validated testing strategies to identify post-TBI deficits quickly and accurately, to circumvent economic realities on the ground in LMICs. We utilized paper tests such as the Montreal cognitive assessment (MoCA), line-bisection, and Bell's test. Furthermore, we combined modifications of neuroscience computer tasks to aid in assessing peripheral vision, memory, and analytical accuracies. Data from seventy-one subjects (51 patients and 20 controls, 15 females and 56 males) from 4 hospitals in Ethiopia are presented. The traumatic brain injury group consists of 17 mild, 28 moderate, and 8 severe patients (based on the initial Glasgow Comma Score). Controls are age and education-matched subjects (no known history of TBI, brain lesions, or spatial neglect symptoms).

Results: We found these neurophysiological methods can: 1) be implemented in LMICs and 2) test impairments caused by TBI, which generally affect brain processing speed, memory, and both executive and cognitive controls.

Discussion: The main findings indicate that these examinations can identify several deficits, especially the MoCA test. These tests show great promise to assist in the evaluation of TBI patients and support the establishment of dedicated rehabilitation centers. Our next steps will be expansion of the cohort size and application of the tests to other settings.

KEYWORDS

traumatic brain injury, TBI assessment, brain injury assessment, TBI tests, LMIC brain injury

Introduction

Traumatic brain injury (TBI) is a type of acquired brain injury due to sudden trauma from objects hitting the head with or without actual skull fracture. It can cause brain tissue damage and functional deficits (1).

The Centers for Disease Control and Prevention (CDC) broadly defines TBI as "an injury that affects how the brain works" (2). The widely accepted approaches use clinical severity to classify TBI as mild, moderate, or severe. Some maintain these severity definitions are arbitrary (3). Accordingly, some classify head injuries, not by their clinical severity, but rather based upon (1) structural damage; (2) mechanism of injury, and even (3) prognosis (4).

TBI is the leading cause of all injury-related deaths and disabilities within low to middle-income countries (LMICs), and according to the 2017 publication from the Lancet Neurology Commission TBI will remain within the top three causes of injury-related death and disability until 2030 (6).

LMICs account for 85% of the world's population. Each year, 50 million TBIs occur in LMICs, compared to 18 million in high-income countries (7). Within LMICs, TBI is a significant cause of hospitalization, death, and disability (8, 9), and the mortality rate from TBIs is 3–4 times higher than the reported rate in high-income countries (10). Additionally, LMICs have greater odds of disability and twice as much death from severe TBI (5, 11).

These disparities are discussed here per the standard classification of the severity of TBI, the Glasgow Coma Scale (GCS), which defines GCS of 13–15 as mild, 9–12 as moderate, and 3–8 as severe (12). The situations on the ground (discussed later in the limitations section), such as lack of trained personnel, subject unavailability for long-term follow-up etc., did not allow outcome measures using GCS, Glasgow Outcome Scale (GOS) or the Glasgow Outcome Scale Extended (GOS-E) tests.

GCS is universally used to on acute medical and trauma patients as a tool for objectively describing the extent of impaired consciousness. Using three levels of responsiveness, eye-opening, motor, and verbal responses, the test aggregates its results providing an overall severity and has been incorporated in numerous clinical guidelines and scoring systems for victims of trauma or critical illness. Clinically, GCS is used to help early management such as securing the airway, patient transfer, neuroimaging, discharge, and monitoring clinical course (17). Studies have shown that increased mortality is associated with decreased GCS score (13), with each assessment yielding more information than the aggregate total score (14). This is distinction is further demonstrated by studies which have shown that level of consciousness is not accurately reflected by total GCS scores, suggesting the need to consider individual subscale behaviors and more comprehensive assessments when evaluating TBI severity (15, 16).

Given the fact that GCS scores can be influenced by several factors such as sensory/language barriers, current treatment or other injury effects, this powerful method or other clinical prognostic tools should not be used solely to predict individual patient outcomes (17).

Moreover, the GCS classification system does not account for visual deficits (18), cognitive deficits (19, 20), and cognitive aging (21), all of which can be present either initially or in the immediate post-traumatic period.

These issues can be harsh especially in LMICs where even such classifications cannot made reliably due to factors such as lack of trained professionals, the patient not arriving at the hospital immediately after injury or not being followed properly.

Furthermore, the lack of resources, research efforts, and funding for health care contribute to the disparities of LMIC's compared to high-income countries (9). Although TBI causes half of trauma deaths (22–25), LMICs lack data on head injury in general (26), the morbidity, and mortality, of head injury, causing underestimation of the problems (27).

Moreover, the epidemiology and management strategies of TBI in LMICs only by few studies and TBI patients in LMICs suffer from lack of access to imaging, patient monitoring equipment, surgeons, and rehabilitation services (7).

At the same time, economic responsibilities for self and family members force most patients with mild to moderate TBI to return to work quickly with what are almost certainly undiagnosed post-traumatic cognitive deficits. This could lead to subsequent accidents in their regular jobs of operating cars, taxis, trucks, and other heavy machinery, making consequential decisions, and causing a vicious circle of potentially significant injuries. These chances are high as LMICs have risk factors for TBI causes (such as motor vehicle crashes) which occur at a higher prevalence and getting medical care that address associated health effects does not occur at the same rate as HICs (28).

Given the importance and difficulty of assessing cognitive deficits of TBI patients, we chose Ethiopia as a demonstration site for developing a method for cognitive screening in TBI patients in an LMIC (19, 20). Ethiopia is the second most populous nation in Africa, located in the sub-Saharan region, where the estimated TBI incidence is 801 per 100,000. The mortality rate for severe TBI (severity as determined by the aforementioned GCS scale) is approximately 50% (29, 30). TBI is particularly frequent in younger people (31). Significantly, the country has more than 70 million citizens younger than 30 years of age (32, 33). This fact has contributed to a substantial toll on society ranging due to TBI-related disabilities and deaths (34, 35). Given that Ethiopia's population is predicted to double in the next 30 years, reaching 210 million by 2060 the overall toll from minimal TBI diagnostic workup, monitoring, and rehabilitation and in some cases even under diagnosis of TBI should be expected to be a

Abbreviations: MoCA, Montreal Cognitive Assessment; GCS, Glasgow Coma Scale; IRB, Institutional Review Board; JND, Just noticeable difference; LMIC, Low-to-middle income country; MMSE, Mini-mental state exam; NHS, National Health Service; NIHR, National Institute for Health Research; RGB, red, green and blue colors; RT, response time; RTA, road traffic accident; TBI, traumatic brain injury; WHO, World Health Organization.

substantial heath crisis (36). Studies like this one will be valuable as more LMICs follow the same trend, especially in Africa, where population growth is expected to increase in the next 40–50 years (37).

A recent study in Ethiopia of 4206 deaths brought to the Forensic Pathology Department. Menelik II Hospital has shown that accidents, homicide, and suicide caused 67% of them (38). Of these, accidental death contributed to 40%, of which traffic-related cases were close to 70%. Another postmortem study of almost 10,000 patients, all who died within 72 h of emergency department (ED) presentation revealed that head injury is the most common cause of mortality (21.5%) of all deaths in Ethiopia (39). In the country, the majority of post-traumatic hospital visits are mainly from head injury (34). The two primary sources of TBI are violence and road traffic accidents (RTA) (40). One of the major hospitals receiving these patients involved, Black Lion Specialized Hospital (which is also one of the very few tertiary hospitals giving neurosurgical services in the country), recorded that the commonest cause of death in its ED is head injury (39). A study in Nigeria (the most populous country in Africa) corroborates the same story (41).

Here, we examined the utility of a number of different tests to determine the severity of the cognitive deficits in patients with TBI. We found that the MoCA, which can be administered by easily trained, non-medically educated personnel, was the most effective method for assessing cognitive deficits in TBI patients.

Methods

Database

We studied 51 TBI patients who had follow-up visits in outpatient neurosurgery clinics and 20 controls, all of whom signed a consent form. The cohort had 56 males and 15 females. Age ranged from 14 to 65, with 18 of them being young people (10–24 years of age) and 53 adults [per the World Health Organization (WHO) definition (42)]. The TBI group comprised 17 mild, 28 moderate, and 6 severe patients (based on initial GCS). Several GCS measurements are routinely taken at these hospitals – such as after brain surgery, after days of recovery etc., however all of the TBI classifications in this research used the initial GCS which is administered at admission, post-resuscitation when needed.

The injuries included 22 to either the right or left hemisphere, and 7 bilaterally. The causes of damage were: violence (25 patients), road traffic accidents RTA (19 patients), and falls (7 patients). Controls (20 subjects) are age and education-matched individuals (no known TBI, brain lesions, or spatial neglect symptoms). A table with the full demographic data and paper test results is provided as a Supplementary Appendix A.

We conducted the study in five locations chosen for several reasons, the main ones being geographical coverage and the existence of approved protocols and collaborations. These corresponding hospitals are located in central (Black Lion and AABET, 12 and 46 subjects, respectively), northwestern (Tibebe Ghion, 9 subjects), northeastern (Dessie, 2 subjects), and southern (Hawassa University Teaching and Referral hospital, 2 subjects) parts of Ethiopia.

We performed most of the studies in two hospitals (Black Lion and AABET, 58/71 subjects) in Addis Ababa, the capital of Ethiopia. Black Lion (BL) Hospital is the biggest referral public hospital in Ethiopia (43). The country's primary health care establishments use referral systems to provide access to community-based health centers before higher hospitals and care options are considered (44).

AABET Hospital is one of the few tertiary hospitals in the country that provides emergency and critical care, orthopedic, neurosurgery, general, and plastic surgery services (45) and it is the only major trauma center in Addis Ababa (46).

Tibebe Ghion Comprehensive Specialized Hospital (TGCSH) is a regional center located in Bahir Dar (the capital city of Amhara National Regional State) in the northwestern part of the country, 565 km from Addis Ababa. The hospital provides different medical services to more than 5 million people in the region (13, 47).

Dessie Referral Hospital (DRH) is one of the largest and frontline public hospitals in Ethiopia's northeastern part (in Dessie, the administrative town of South Wollo zone), 400 km from Addis Ababa (48). It is a referral hospital serving close to 5 million people (49).

Hawassa University Referral Hospital (HURH) is a tertiary-level hospital located in Hawassa, the capital city of southern Ethiopia (275 km to the south of Addis Ababa). It serves around 12 million people in the Southern Nations, Nationalities, and People Region (SNNPR) and the neighboring Oromia region (50).

The breakdown of subject categories per hospital are as follows: AABET 12 controls and 34 tests, BL 8 tests and 4 controls, TGCSH 5 tests and 3 controls, both DRH 2 tests each.

Testing environment and data collected

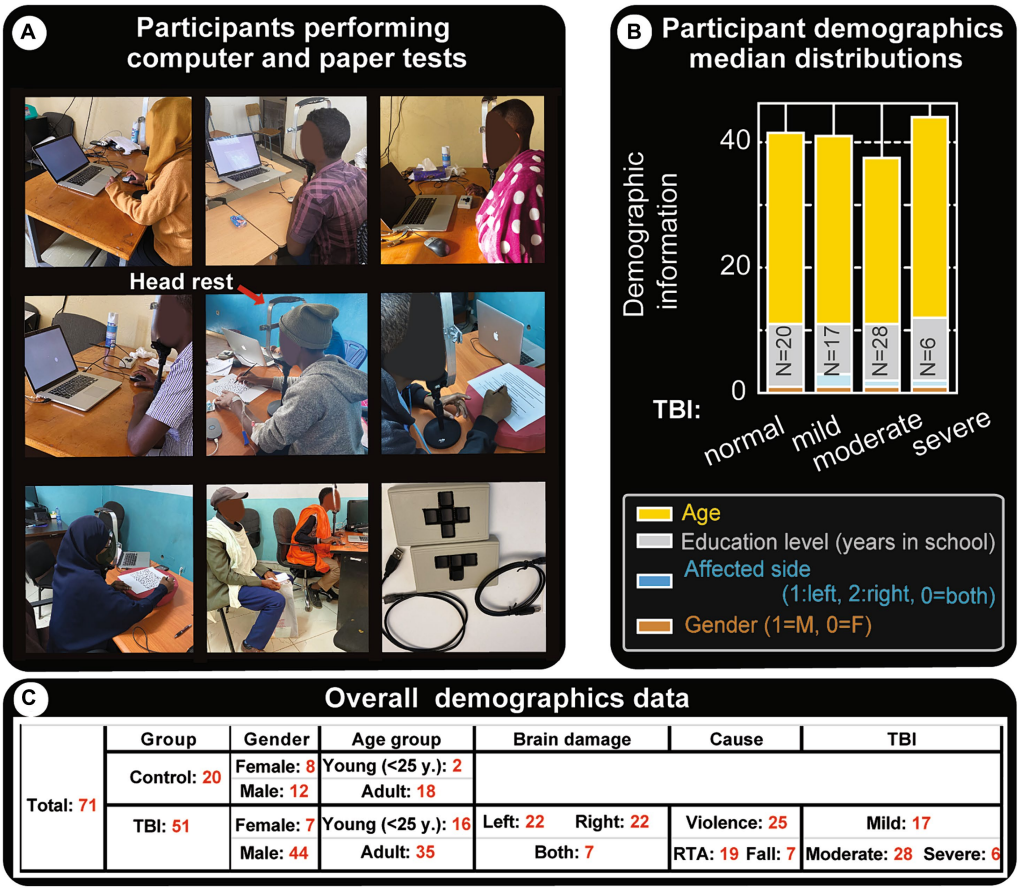
We administered all tests in routine patient evaluation rooms in the corresponding clinics. At least one family member was available to verify demographic and other information before the start of the experiments. After the verification procedure the subjects were not allowed to interact with their families or other participants until after the testing session was completed.

Given the possibility that most subjects have yet to gain experience with paper tests or computer knowledge, we described the tasks in depth. The tests started when the examiner was sure the subjects were able to perform both the paper tests and computer operations without impediment.

All subjects were briefed on experiment goals and procedures and signed a consent form as determined by the specifics of the IRBs. All participants verbally agreed to be photographed and videotaped for educational purposes.

Each session lasted approximately 30–45 min with 3–4 breaks lasting an average of 5 min. Subjects could request a break or terminate the experiment at any time. We did not perform any invasive procedures or administer any medication.

Figure 1A shows research subjects performing paper and computer tasks. Head/chin restraints were used to keep subjects from moving their heads during paper and computer tests (red arrow in Figure 1A, middle panel). This apparatus kept the eyes at ~50 cm from the paper or computer screen. A computer mouse and a novel four-key mini keyboard input instrument specifically made for this study (Figure 1A, last panel) were used by subjects to respond to questions without repeated searching or looking down at the keyboard after initial instruction. For computer tests, each subject was provided with initial training and assessment before administering the actual test. If the subject had any difficulty understanding or performing the task, he/she did not move onto the actual task. For some subjects this meant



	Group	Gender	Age group	Brain damage	Cause	TBI
Total: 71	Control: 20	Female: 8	Young (<25 y.): 2			
		Male: 12	Adult: 18			
	TBI: 51	Female: 7	Young (<25 y.): 16	Left: 22 Right: 22	Violence: 25	Mild: 17
		Male: 44	Adult: 35	Both: 7	RTA: 19 Fall: 7	Moderate: 28 Severe: 6

FIGURE 1
Demographics and experimental settings. **(A)** Snapshots of subjects as they perform paper and computer tests. The experiments are run in regular hospital office settings with at least one family member present to assist with initial interactions, without helping the subject with test performance. The subjects are instructed on what to do and data collection is started once they are confident. In general, the tests require visual focus in the center of their visual field (the center of the screen in computer tests) and have to keep their head from swaying. However, most subjects had difficulties following instructions to not move their heads during the sessions, therefore a chin/head restraint was used (indicated by the red arrow in the middle panel). Bottom right panel shows custom-made 3 and 4 key USB mini computer keyboards that were used for capturing their responses. **(B)** Clinical data and demographics of patients with TBI. This panel shows the type of TBI and median distributions for age, education level, affected brain side and gender. Effort has been made to get more or less comparable representations for these parameters and for each TBI group. Similar heights in the category bar charts indicate the cohorts are fairly balanced. **(C)** Clinical data and demographics: tabular representation of major attributes of participants.

the computer tests went a little beyond the average 30 min per session and ended up being close to 45 min.

In addition to test performance, clinical data such as time since injury, cause of TBI, and other contributing factors such as alcohol use were also collected.

Tests

The following conventional/novel clinical vision, memory, and spatial neglect tests were used (ranked in order of ease and overall order of administration).

Paper tests

We used and scored three internationally validated paper tests.

Montreal cognitive assessment: this internationally-validated assessment evaluates cognitive function and it includes tests of orientation, attention, memory, language, and visual–spatial skills. For this project, it has been officially and professionally translated into the national language of Ethiopia (Amharic) (currently available at MoCA's official website: https://www.MoCAtest.org) (see Figure 2). The translation included necessary changes for cultural appropriateness. We used this new version for all subjects and consistently administered it as the first test.

Because spatial neglect commonly causes problems in daily routines such as crossing the street, we decided to assess spatial neglect. The other two paper tests used are the most common clinical tools to assess spatial neglect, both probing the same underlying cortical deficits (51).

1 Bell's Target Cancelation task (52) (spatial neglect task 1): this is a visual search and mark task on an A4 size sheet of paper, which has 40 distractors & five targets (bells) in each of seven invisible columns. Patients circle all bells, and a score is created from the difference in omissions on ipsi-minus contra-lateral sides (Figure 3). Three or more ipsilateral vs. contralateral omissions are taken as having spatial neglect (23). To

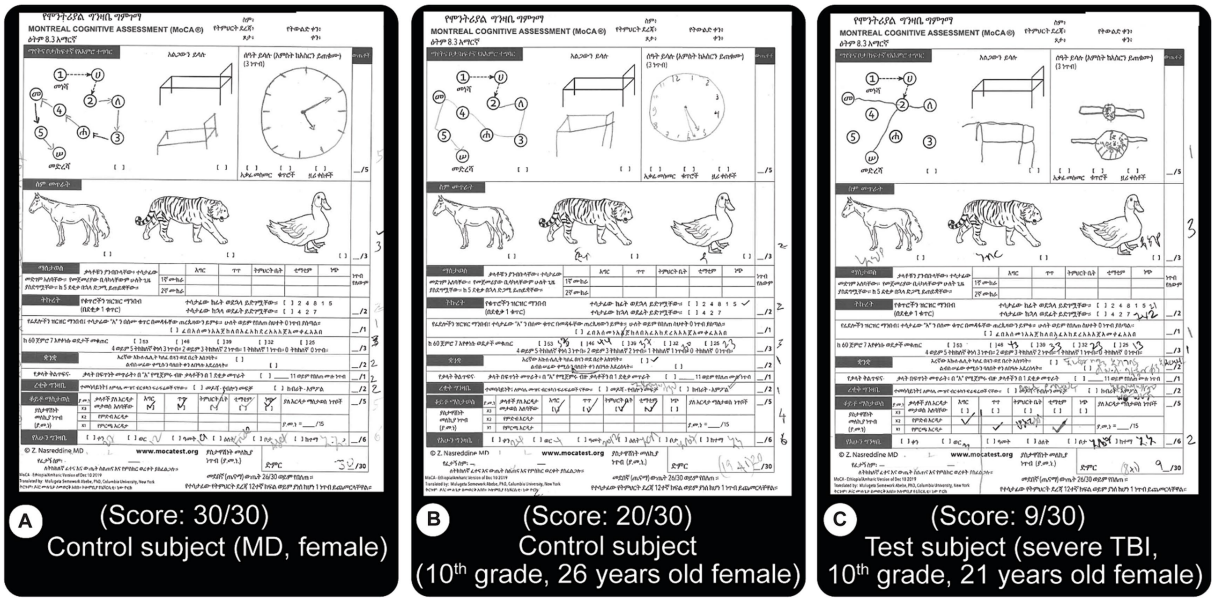


FIGURE 2
MoCA test results. This test is an internationally validated tool that focuses on motor, memory, language, concentration and orientation performances. Subjects are asked to perform different tasks such as to draw lines from a letter to a number, both increasing, draw objects from memory, name displayed animals, recall specific words, etc. The version used here is an official translation of the test to the national language of Ethiopia, Amharic. A score of 26 or more out of the possible 30 is considered normal. **(A)** Normal score from a control subject (MD level education). **(B)** Close to good score (20/30) result from a control subject **(C)** Test result from a patient with severe TBI showing a lower score (9/30). Both **(B,C)** have 10th grade education. Most of the errors from TBI patients were related to memory issues.

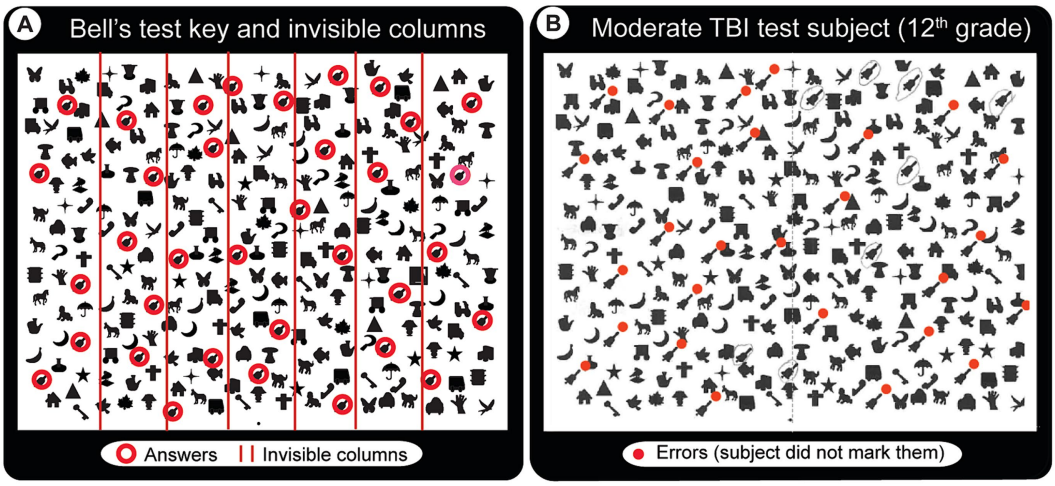


FIGURE 3
Bell's test solution key and a sample result from a patient with moderate TBI. The task requires locating and drawing a line around each of the bell-shaped images in an array of other images without moving the head. **(A)** Solution key. Red circles (not visible in the actual test paper) indicate the 35 bells that the subject has to find and circle. They are laid randomly in 7 invisible columns (5 per column, red lines indicate the column boundaries). **(B)** Abnormal Bell's test result from a patient with moderate TBI who appears to have spatial neglect mainly for the lower left visual field (red dots indicate missed bells).

accomplish this (and make the test usable by the local population), we created a new version of the Bell's test by making an entirely new library of images to Figure 3.

2 Line-bisection task (53) (spatial neglect task 2): the patient makes a small pencil mark in the middle point of each of the multiple lines with varying lengths on A4 size paper. Left visual neglect will cause subjects to make right-ward errors, and vice versa for right neglect. In the classic line-bisection task (53), the patient makes a small pencil mark in the middle of each of the 20 lines with varying lengths (100, 120, 140, 150160, 180, and 200 mm). Deviation percentages over all lines (both left and right deviations)

are scored. Having an ipsilesional deviation above 9.5 percent is defined as having spatial neglect. This number is selected because it had a confidence interval above 99% for the control group (42). In our initial test, data from the first 10 subjects made it clear that short (18 mm) slanted lines were inadequate or very ineffective in evaluating deviations. With the extended horizontal line version utilized, we found discernible differences within and between patient and control subject groups (Figure 4). For simplicity and clarity, the data presented here uses the simple metrics of summing up of all negative and positive errors (millimeters away from an ideal middle). After we gather statistically valid control data, the deviation percentage method will be utilized.

Computer based tests

We wrote 6 computer based tests specifically for this study in Python which we tested on 10 volunteers before using them on study subjects (Figure 5) – prior to any real data recording.

At the start of each of the 6 computer tests, the experimenter described the task verbally and demonstrated a few trials. Once the subject is confident, a graphic display describes the task and user interaction guidelines once more and all efforts are made to maximize performance. For example, in the Just Noticeable Difference (JND) task (Figure 5D), a user must press the left or right arrow keys to select which of the images (Gabor patches) presented, on either side of a central fixation cross is not slanted. Our custom keyboards allowed for the subjects to signal a rapid response.

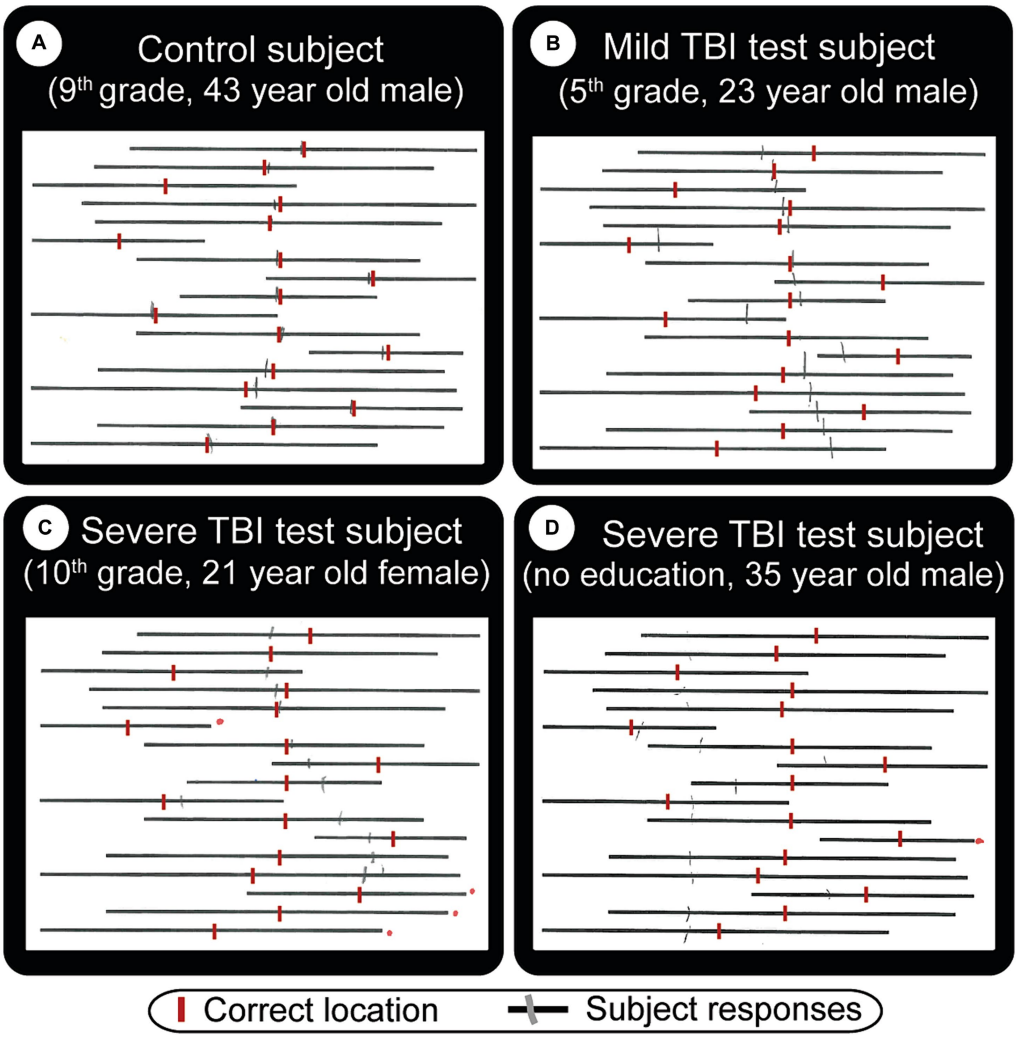


FIGURE 4
Straight line bisection test result examples. The subject's task is to draw a vertical tick mark where he/she thinks the middle point of each line is. These are indicated by red vertical lines (manually added here for visual comparison). Gray (pencil) lines are actual subject responses. Depending on what kind of visual problems the subject has, the middle point can be difficult to estimate. **(A)** Normal subject who shows minor errors. TBI patients (**B**, mild) and (**C**, severe) show strong cases of left neglect, in that they both made lines that are mostly to the right of the ideal location. Subject **(C)** did not cross 4 lines (red dots to the right of missed lines). **(D)** Severe TBI patient with right neglect, who also missed one line, has a very big total error (errors are easier to see in Figure 8B).

FIGURE 5
Screen captures (real-time snapshots) of computer test instructions and actual experiments as they are being administered. Once the participant expresses confidence in taking the test, the experiment is started with the first display being the written instructions (red-boxed, top panels in each test panel) followed by the actual experiment (gray-boxed, bottom panels). The subjects wait for a central target to appear and are instructed to keep their eyes focused there while using peripheral vision to perform the tasks and respond with a mouse movement and click or custom keyboard click. Experiments are self-terminated when all trials are completed. **(A)** Vision and memory-guided clicks: move the mouse to a target location where a circular stimulus appears randomly while it is still displayed (visual), or once it appears quickly and disappears (memory). **(B)** Color discrimination: red, green and blue circles appear left, above or right of fixation or at random location and order and the subject has to click the left, up or right arrow keys for red, green and blue colors, respectively. All subjects are tested for color-blindness to these colors and none of the subjects had difficulties separately identifying them. **(C)** Number comparison: click left arrow key if the number you just saw is smaller than the number that was quickly displayed a moment ago, or the right arrow key if it is greater. **(D)** Just-noticeable differences (JNDs): two circular images filled with nearly/vertical bars (Gabor patches) are displayed left and right of the central fixation point. Click the left or right arrow key if the left or right image is vertical, respectively. **(E)** Stroop test: this task measures the level of accuracy in dissociating color from information a given text displays. For instance, in this snapshot, the Ethiopian (Amharic) word displayed stands for 'red' but it is written in blue. The subject has to press the right arrow key which represents the color blue, not the left one which represents red color. **(F)** Phase-loop: press the left arrow key if the image seems to rotate left, or right arrow key if it is perceived to move to the right.

1 Visual and Memory Performance (Figure 5A): measured with both vision and memory-guided hand movements. Subjects are asked to visually fixate in a middle location in a computer screen (center of visual field) until a circular target appears in random locations on the computer screen. For visual targets, the subject moves a mouse cursor to the peripheral target that has just appeared and clicks inside the visible circle. The memory task requires the subject to make the same response to a briefly presented target. The subjects performance is measured by click location accuracy.
2 Color Discrimination: Color experiments tested the capacity to discern red, green, and blue colors (RGB) using the left, top, and right arrow keys, respectively. There were three versions: (1) Color center (RGB): colored circles appearing at the center of the screen; (2) Color Left–right (LR): colored circles appearing left or right of a central fixation cross; (3) Color Left–right-UP (LRU): colored circles appearing left, above or right of a central fixation cross; (4) Color random (RGB): colored circles appearing in random locations in the computer screen.
3 Just Noticeable Differences (JND) (slanted Gabor patches), choosing the image which is perfectly vertical compared to another image just on the other side of a fixation cross. The fixation cross is located on the center of the screen (Figure 5D).
4 Color and Word Dissociation (Stroop tests) choose and respond to the color of a word you see on the screen, ignoring the word. For instance, the subject press the left arrow key for red color even if the work reads "blue" (written in Amharic letters) (Figure 5E).
5 Motion and Contrast Perception (object rotation, phase loop): press the left or right arrow key depending on which way the subject thinks the central image is rotating. This test also includes various illumination levels (to test contrast sensitivity) and rotation speeds (Figure 5F).
6 Math operations: simple numbers comparison: the subject is instructed to press the left arrow key if the number seen earlier is smaller than the one number most recently seen; Otherwise, press the right arrow key (Figure 5C).

Results

For relatively fair comparisons, similar participants were included to the different groups (shown in Figure 1B). This study includes 71 subjects (51 patients and 20 controls) (see table in Figure 1C). The median distributions of the most important metrics, age, education level, and affected brain side, are comparable. However, gender is mostly male-dominated (56 versus 15), consistent with world data [some studies conclude the chances of sustaining TBI are 2.22 in males than females (42, 54)].

The MoCA was the most accurate and specific test in evaluating TBI-induced deficiencies, especially memory and general executive thinking deficits. The test corrects for education, i.e., by adding a point to the total score if the subject has 12 years of education or fewer.

We found TBI severity correlated with reduced test performance. Figure 2 depicts these observations. A control subject with high education (medical doctor) received a perfect score (30/30, Figure 2A, above 26 is considered 'normal.' i.e., control). Another subject with a 10th-grade education scored below control (20/30). A severe TBI patient (C) scored low (9/30), although both Figures 2B,C have 10th-grade education, are female and are close in age (26 and 21 respectively). For all subjects, this test clearly stratified performances better than others, as shown in the other figures, such as Figures 6A, 7A.

Bell's test

In Bell's test, subjects must find and circle all 35 bell-shaped images (circled red in Figure 3A). The test seems very easy for most subjects despite their conditions, except for the minor indication that controls and mild TBI patients have more or less compact response ranges (oscillating around the maximum score of 35, see Figure 6C). Nevertheless, there were a few clear examples, such as a moderate TBI patient who missed many bells around the left bottom half of the image maze (in Figure 3B, red dots indicate missed ones), suggesting spatial neglect of the left bottom quadrant of the visual field.

Line-bisection test

The line-bisection test performs well (second best paper test, first being MoCA), especially in finding visual deficits. Figures 4B,C exhibit severe cases of left-sided neglect, Figure 4D a right-sided neglect, while Figure 4A, a control subject, shows only a few minor errors. Figures 4C,D also failed to cross the lines numbered 4 and 1, respectively (red dots on the right side of the paper denote missed lines).

Education level and paper tests

Results in this area were classified by education level and TBI to assess bias in the paper test. Figure 8A confirms that MoCA displays an educational effect, and it behaves the same way for all classes of TBI. i.e. higher education level corresponds to better performance. Line-bisection (Figures 8B, 6B) and Bell's test (Figures 8C, 6C) both show that control subjects have a stable error distribution and test performance, respectively with limited education effect. For line-bisection, control subject errors stay around 0 and are less chaotic in their distribution (in comparison, the subject in Figure 4D, showed huge negative errors).

A deeper look at the relationship between TBI categories, paper tests, and education level is depicted by boxplots in Figure 6. As a general indication of the trends the data is going toward, the figure shows statistical results from multiple comparisons between the categories performed using Mann–Whitney tests with Bonferroni corrections. This approach is used when a nonparametric test is required to compare two independent groups (i.e., to test whether two samples are likely to derive from the same population). A nonparametric test is chosen also because of the small sample size, which makes it difficult to be certain about the kind of distribution the general population has. The boxplots in Figure 6 show that the medians (which this test compares) vary between groups. The level of certainty (differences) is depicted by asterisks ('*') or 'ns' (no significant differences) as shown in the cartoon in the bottom right.

Almost all paired comparisons show significant differences, especially when TBI groups are compared to controls.

MoCA results (Figure 6A) indicate that TBI severity decreases test performance. Control subjects have higher scores, near symmetric whiskers, and a slight positive skewness.

Figure 6B summarizes the line-bisection test scores versus TBI level. The boxplots are plotted against a *Y*-axis which depicts the difference between counts of right (positive) crossings of the ideal middle for each line minus negatively skewed crossings. In other words, more negatively skewed crossings indicate possible right-sided neglect. Here, as in the other tests, it is imperative to not overinterpret the statistical significances as concrete proofs but rather as early indications of trends that will need to be proven at a later time when larger data sets are available.

Bell's test score versus TBI does not show a major effect (Figures 8C, 6C). Education level does not appear to be related to TBI damage, except that controls tend to have higher education (Figure 6D), possibly due to one or more of several reasons. As shown in Figure 6E, alcohol consumption is not similar between the different groups (for instance controls tend to be the least consumers), although the present sample size does not warrant profound conclusions.

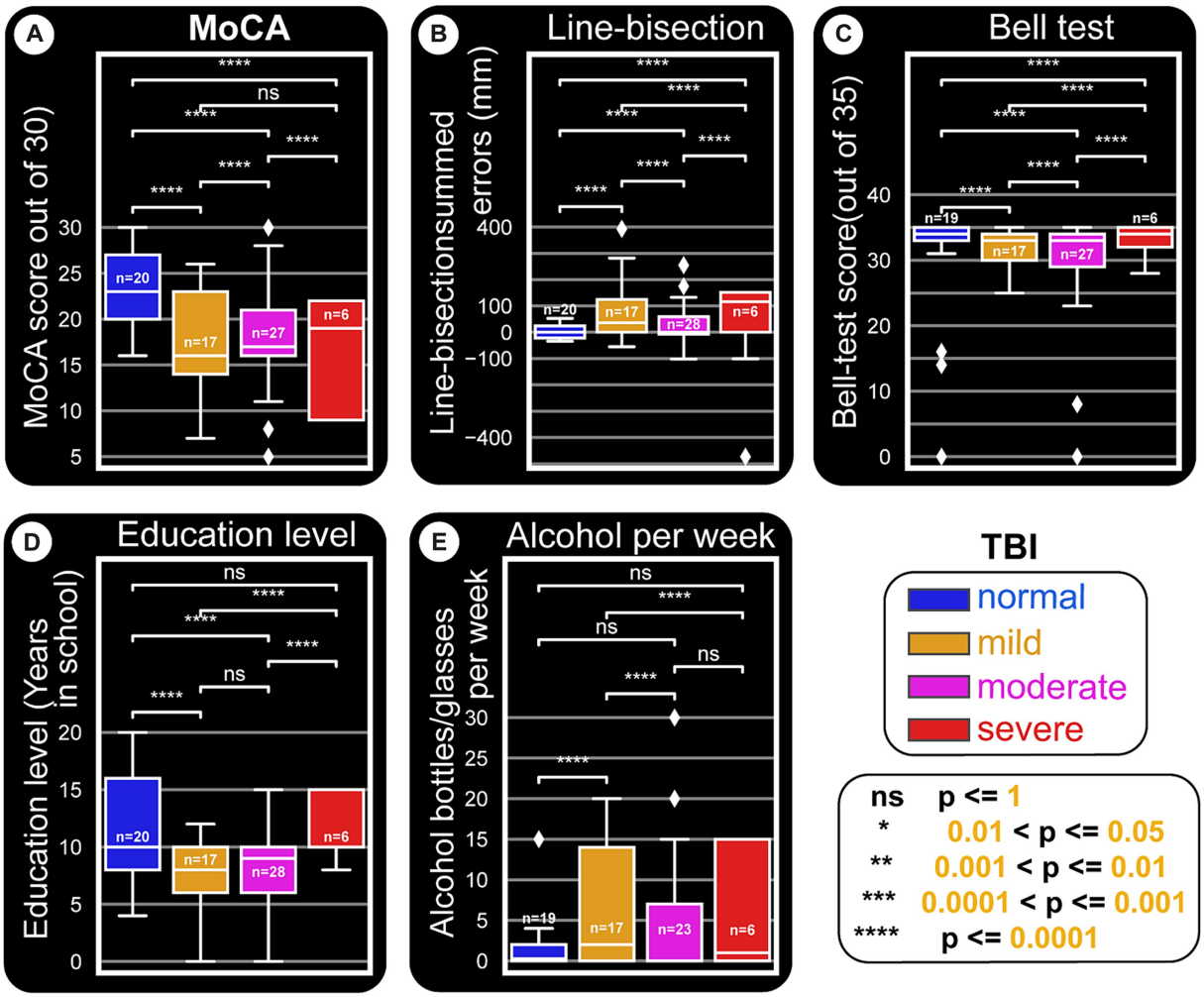


FIGURE 6
Paper tests and education level and their relationships with TBI types. This distribution figure uses box plots to compare quantitative data from different variables. Straight line segments above each pair of boxes connect significantly different as shown by *p*-values from Mann–Whitney-Wilcoxon two-sided test. The level of these differences are depicted by asterisks ('*') or 'ns' (not significant). As in other figures, all *x*-axes are set to the main categorization used: TBI kind (normal, mild, moderate and severe). The three quartile values of each distribution are shown by the boxes and the rest of the distribution is presented by the whiskers. These whiskers extend to observations that are within 1.5 interquartile-ranges of the lower and the upper quartile. The mid-point of the data (middle quartile, also called the median) is indicated the middle line in the boxplot that divides the two parts of the box. Outliers are shown by diamond points. **(A)** MoCA score is reduced with severity of TBI damages. **(B)** Line-bisection test scores. The boxplots are plotted against a *y*-axis which depicts the cumulative errors for all line crossings that are left (negative) or right (positive) of the ideal middle for each line. Accordingly, more positively skewed crossings indicate possible left neglect. It appears that patient groups tend to be right or left skewed, owing to the majority of the side of the brain damaged for the cohort. **(C)** Bell's test score versus TBI damages does not seem to show major differences. However, as in Figures 8B,C, normal subjects seem to have a stable error distribution, while patients (especially moderate and severe TBI ones) show wider and skewed boxplots. **(D)** Education level also seem to be related to TBI damage, in that normal subjects tend to have higher education. Whether this points to a major predisposition to get into TBI situations remains to be seen. **(E)** The amount of alcohol consumed per week appears to be positively related to having TBI in general.

10.3389/fneur.2024.1397625

Computer test results

Almost all subjects were also tested on computer games measuring vision, memory, math, and other functions. The results were compared to paper tests and other metrics to understand similarities, differences, and interactions. Figure 7 summarizes these findings by using categorical line plots. Each computer test result is plotted against a paper test or another variable to show the central tendency of the data points (their mean) and the errors around them. They show how each outcome changes based on the different TBI categories. For instance, we can investigate how Stroop test results change with the TBI category, how they compare with MoCA results and what their relationship with the same categories is. Imagine each line as a group data (mean) for subjects who took that computer test.

The first and most significant finding is that the tests are performed dissimilarly, and test accuracy decreases with TBI severity. Figure 7E depicts test accuracy (correctness). Y-axis indicates the average accuracy (scaled 0 to 1) for the given cohort. The score of "1" indicates all group members (for example, control subjects doing RGB task) scored perfectly. We observe that for each cohort and test type, the standard error around the mean performance increases with TBI severity (indicating variability in individual deficits).

Almost all computer test results show a declining MoCA score as TBI severity increases. This relationship between a computer test and TBI category is one of our most precise results and is shown in Figure 7A. Individual performance on MoCA tracks performance on all computer tests.

Figure 7B plots computer test results against line-bisection errors. Two observations are worth noting here. (1) Control subjects have similar results for each test and less error around the mean values. (2) TBI groups show inter-test variability and larger errors around the mean for each test. The same two general observations hold for Bell's test (Figure 7C) with one caveat. With Bell's test, control subjects perform differentially on each computer test. Whether this is due to their better visual performance (which this test examines) or any other reason remains to be seen.

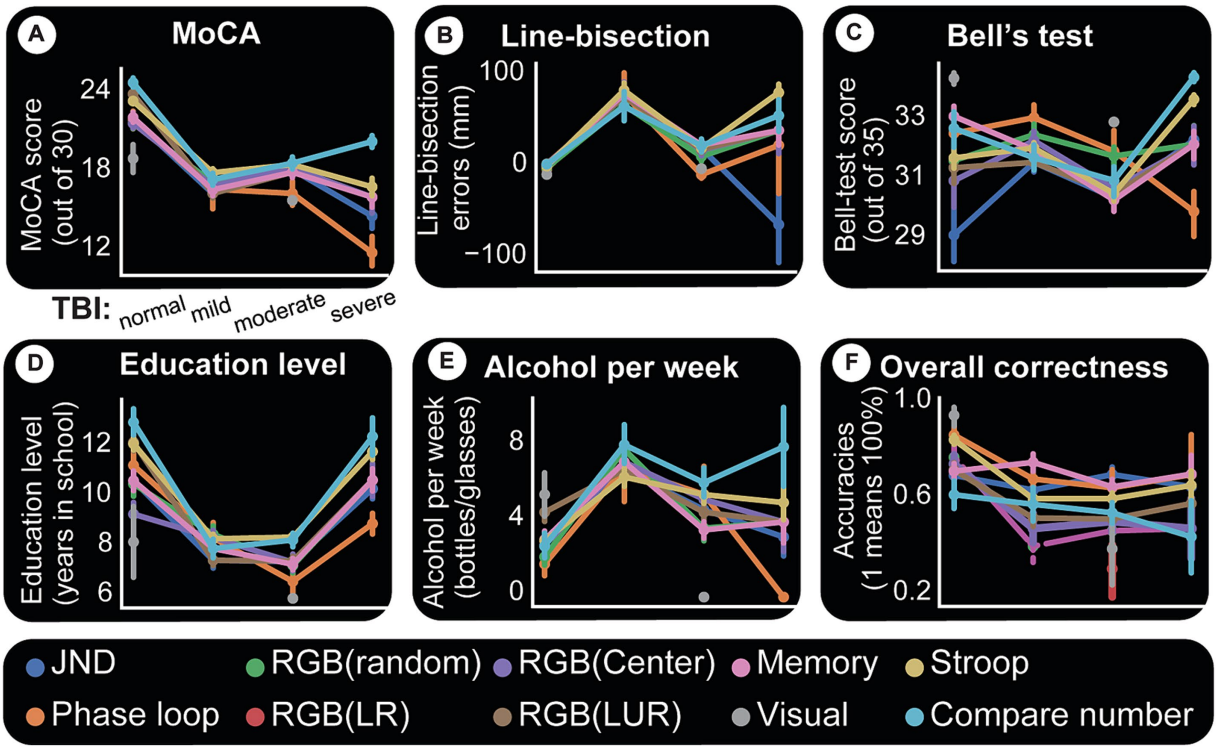


FIGURE 7
Computer tests and their relationships with paper tests and accuracies. For all panels, *x*-axis is TBI category. Each colored line indicates a specific computer test. Each point in a given line is the mean paper test performance response for the given TBI group (*x*-axis) and for the subjects who took that particular computer test. The uncertainty of the estimate is shown by whiskers (indicating standard error). A simple way to understand this figure is to look at panel **(A)** and see that the central tendency for MoCA scores and all computer tests is to decline with TBI severity. This same panel shows that there is more certainty about this assumption because the standard errors are small. **(A)** MoCA test appears to affect all computer test results relatively the same way. **(B)** Line-bisection performance also seems to follow TBI trends except perhaps number comparisons which show a slight difference for mild patients. **(C)** Bell's test. One possibly important observation here is a clear spread for normal subjects in performances for different computer tests, indicating better task discriminations. **(D)** Computer tests and accuracy (correctness). *Y*-axis indicates the average accuracy (scaled 0 to 1) for the given cohort. A score of "1" indicates all members of a given group (say normal subjects doing Stroop task) had a perfect 100% accuracy. Overall, TBI appears to cause decline in accuracy and more variability in performance (as shown by whiskers for each category and computer test). Normal subjects perform better in all computer tests, followed by mild TBI patients, etc. **(E)** Alcohol consumption data points to the presence of discernability for computer tests and TBI categories. It is interesting to note here that the two time-consuming tasks, Stroop test and number comparisons, seem to be more discriminatory of TBI categories using alcohol consumption. **(F)** Computer tests and accuracy (correctness). *Y*-axis indicates the average accuracy (scaled 0 to 1) for the given cohort. A score of "1" indicates all members of a given group (say normal subjects doing Stroop task) had a perfect 100% accuracy. Overall, TBI appears to cause decline in accuracy and more variability in performance (as shown by whiskers for each category and computer test).

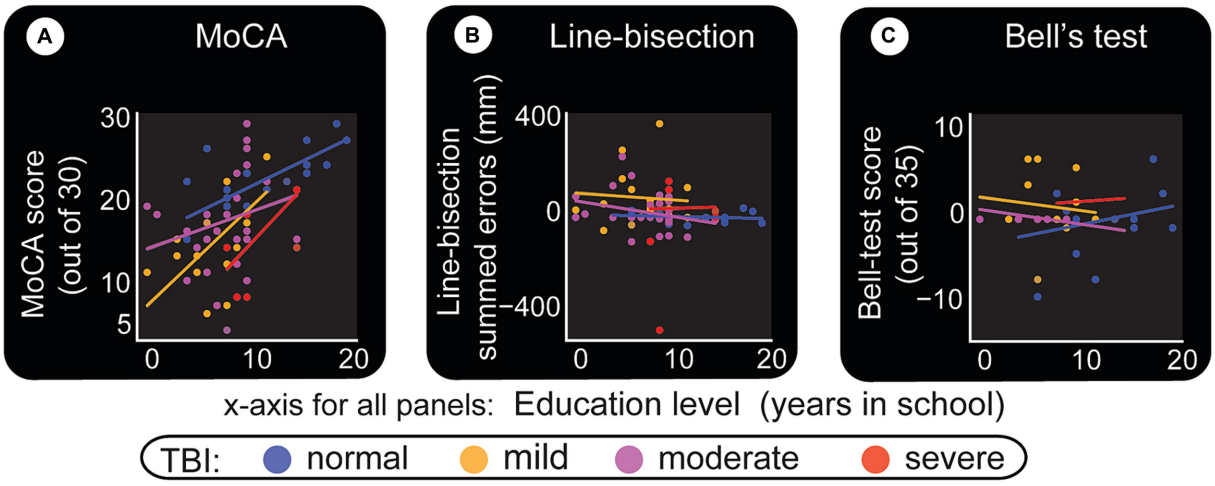


FIGURE 8
Level of education and its relationship with paper test performance. Level of education as described by years in school is the x-axis for all panels. **(A)** MoCA test. Despite the limited number of participants, this test shows an education effect, but similar for all classes of TBI. **(B)** Line-bisection test. Y-axis quantifies the sum of all errors (in millimeters) that are to the left (negative) and right (positive) of the ideal middle point. More positive numbers indicate left neglect. **(C)** Bell's test. A score of 35 indicates that the subject has found and circled all bell-shaped images. This result indicates that most can perform the test relatively well. It is interesting to note however that, for both line-bisection and Bell's tests, normal subjects appear to have similar (stable) responses at all education levels. Also, there seem to be minimal line-bisection errors [errors are around 0 to +/− 50 pixels in **(B)**, also see Figure 6B]. Note the one outlier severe TBI patient with right neglect (actual test result shown in Figure 4D). Bell's test results for normal subjects also appear to have a straight fit line that hovers approximately above 30 (also see Figure 6C).

Visually and memory-guided hand movement errors

Next, we look at vision and memory-guided movements, two brain functions whose disruptions often cause serious life complications in TBI patients. The results indicate that visually-guided hand movements are more accurate.

The subject is required to move the cursor to the center of the target circle and click. Thus, error is measured as the distance between this ideal coordinate and the response (end point). Error distributions for visual and memory tasks show two primary effects: (1) controls make fewer errors; (2) patients' errors are larger (Figure 9). End-points (blue for controls and red for patients) in panels Figures 9A,D are numerous and far from the invisible target circles (white) for the TBI victims. These differences are shown by error lines drawn between the target and response. It is visually clear that controls have a more or less similar error profile (Figures 9B,E), while the patient group makes longer errors even in visual experiments (Figure 9C) and an effect more pronounced in the memory version (visually compare Figure 9C and Figure 9F). This is summarized in Figure 10A, which displays the mean values for each TBI group and experiment. It shows an increasing trend based on injury severity and that memory errors are about twice that of visually-guided responses (for all TBI groups).

Computer test response times

Computers allow us to measure subjects' response speed, which can be affected by factors such as task difficulty, visual and/or motor deficits, age, etc. The computer tests show an overall increase in response time (RT) as TBI severity goes up (Figure 10B).

Discussion

Given the lack of trained professionals and modern diagnostic tests/devices, such as diffuse tensor imaging, x-rays, and CT scans, the projected increasing burden from TBIs and subsequent disabilities within LMICs, and the likelihood that such deficits will in turn lead to work-related accidents or injuries, developing simple, accurate, and scientifically based tests that help identify post-TBI deficits is essential. These tests should be simple, affordable, and give the clinician meaningful and accurate evidence of measurable neurological TBI related deficits. This information can assist clinicians to isolate TBI patients with either memory or visual deficits, or both who may benefit from close follow-up and rehabilitation before returning to work.

Our results from both paper and computer tests show a similar trend - that TBI severity reduces performance in all tests.

It is important to make clear that the tests and results are not to be taken as adequate and conclusive. There are few points to consider in pushing the research forward. First, the situation on the ground in Ethiopia did not allow to repeatedly bring patients back to the hospitals and perform a longitudinal study as most subjects traveled hours and some even days to be tested.

Second, patients that could be included were in various, post-TBI stages days to months and had a mix of mild, moderate, and severe TBI levels, making it hard to come up with a sample size to cover the full time frame and the three levels on TBI injury. These two challenges are demonstrated in the figure in Supplementary Appendix B, which shows at the time of test administration injury from 1 day to 115 days on average is included in the patient population. The length of injury contained most (38/51) below the 75th percentile for the cohort (240 days since injury), and 50th percentile is 115 days. All TBI groups have a more-or-less similar distribution.

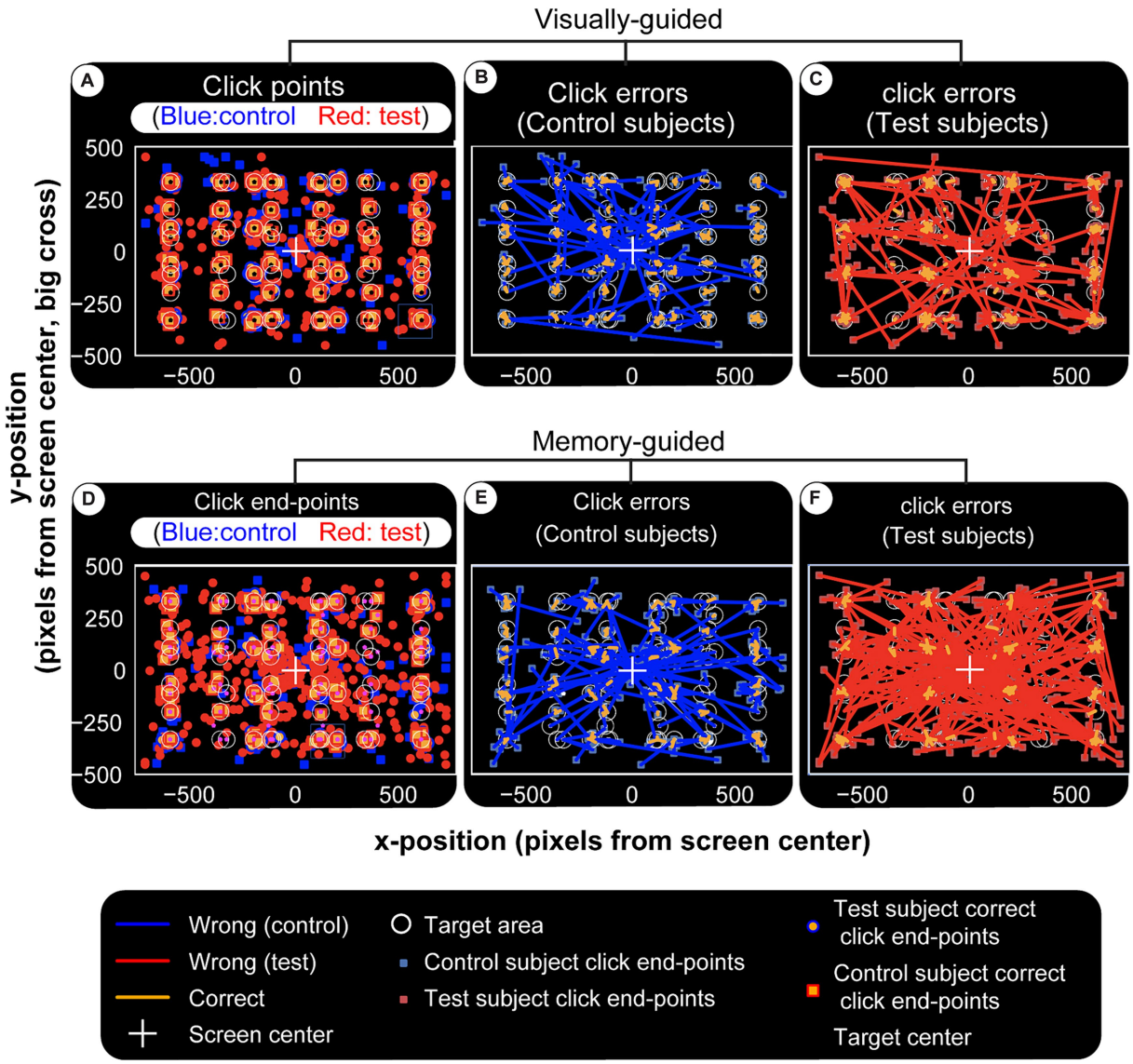


FIGURE 9
Visual and memory-guided click errors. Subjects are required to hold the computer cursur at the center of the screen (big white cross) and move to a 40 pixel radius circular visual target (white circles) when it appears in a random location. They reach to it with the cursor while it is still on (visual) or after it disappears (memory). Once at the target location, the subject clicks the mouse, trial ends. Blue squares and red circles indicate wrong click points (outside the targer area) for control and test subjects, respectively. After a random inter-trial interval, the central fixation cross appears again for th next trial, with the computer cursor automatically reset to the same location. Panel **(A–C)** are for visual and **(D–F)** are for memory-guided experiments. **(A,D)** Show correct and wrong click points. Blue and red lines in **(B,C,E,F)** are drawn from the actual click points to where they were supposed to be made. They depict the maginitude of the errors (distance from center of target circle) for visual and memory targets in controls and test subjects, respectively. While both groups make larger errors for memorized targets, test subjects (patients) have higher error rates and magnitudes, again especially for memory targets. Visually **(F)** is more crowded than **(E)** and this error magnitude is quantified in Figure 10A.

These two main obstacles made it impossible to perform the tests repeatedly on a single subject and also to include other examinations like those which probe post-traumatic amnesia (PTA). However, the implemented tests are good starting points and mostly deal with the important questions, for instance, MoCA indirectly covers most of the PTA questions.

In keeping with its reputation, the MoCA test resulted in a clear separation between control and various TBI groups. All analysis points toward a possible use in the clinic for testing a few important brain functions such as comprehension, memory, and simple math.

Some tests, such as Bell's test, show inferior performance, perhaps because there were only 71 subjects in this study and also due to TBI related reasons. For instance, Figures 4B–D (the line-bisection test) and a few other patients, although they are otherwise visually normal and can make a few correct cancelations, seem to make impulsive decisions and hastily cross the lines in what appears to be a straightforward pattern, with similar horizontal location for all lines.

Despite the experiments being designed to test different mental and visual capacities, TBI patients may follow the same strategy to

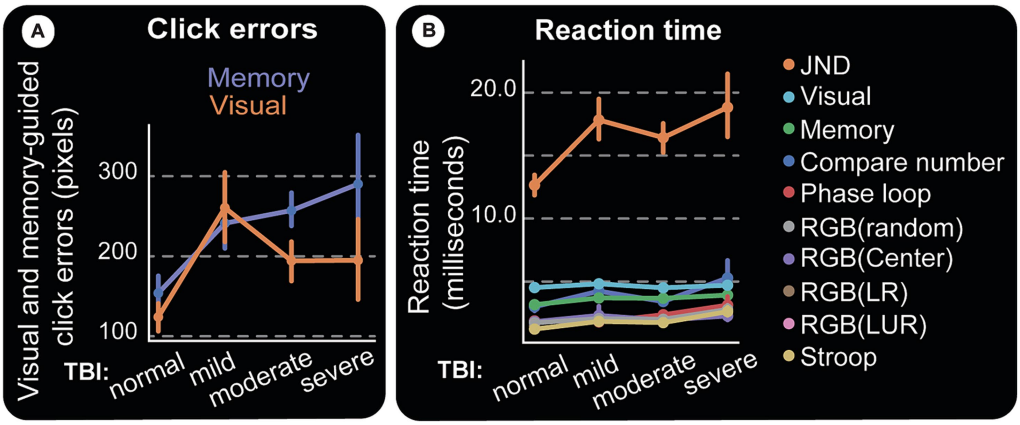


FIGURE 10
Clicking errors and reaction time. **(A)** Magnitudes of vision and memory-guided click errors away from the center of the target circle. Moderate and severe TBI subjects have almost twice as much errors as control subjects, especially for memory-guided clicks. **(B)** Reaction Time. Response time (RT) starts at stimulus presentation, includes reaction and movement time, until the completion of the required response. For instance, deciding which one of two almost similar images that appear flanking a central fixation point is not slanted (our JND experiment), is a difficult task and should take a long time. Indeed, the figure shows it to be the longest response time computer test amongst all we administered and at least with the limited data we have, does not track TBI.

answer test questions. These could include impulsive and ballistic cursor movements to a visual target to maximize the chances of hitting it without regard to accuracy of where in the large circle the end point is, use the pencil to do a very slow horizontal scanning on Bell's test, keep saying 'higher' for a consecutive numbers comparison test, etc.

One trend we noticed is that mild and moderate TBI patients line-bisection errors seem to reduce with more education (downward slopping green and blue lines in Figure 8B). The word 'trend' is used here to indicate that more subjects need to be included (per our calculations, at least 200 subjects) for statistical power. Multiple comparison tests (Figure 6A) indicate that there are differences that need to be verified further. Once again, tests like MoCA (Figure 9A) and memory-guided hand (computer cursor) movements (Figures 9D,E) indicate deficits caused by TBI.

Depending on which parts of the brain are affected by the specific TBI, visually-guided saccades [which involve early visual areas (55)] could be affected separately from memory-guided saccades, which are slower by about 100 ms and involve more cortical processing and other brain regions (56). The same applies to hand movements. The effects can be even more complicated if the TBI affects an area of the cortex involved in both arm and hand movements. In our results, however, visually guided movements are slower than memory-guided movements (Figure 10B).We attribute this difference in visual vs. memory guided movements to task design for two reasons. First, because subjects were able to plan movements during the memory period. We were only concerned about accuracy. Second, the subjects, especially moderate or severe TBI patients, were impatient and too eager to respond, especially on memory trials.

Computer tests tracked TBI deficits and MoCA performances, suggesting possible objective test development and even future rehabilitation exercise creation.

Most of our patients had injuries from violence than from RTA or alcohol abuse, maleness is a precipitating factor consistent with the data from most of the world (54), in addition to young age and violence. In Ethiopia, a meta-analysis showed that across all studies there is higher proportion of injury in male than female patients (range 53.9–91.2%) and in economically active age groups of 15–59 years (Range 56.4–80%) (34).

These facts call for concerted efforts to change the circumstances and allow improved measures to quantify the outcomes. There is high enthusiasm in the patient population, practicing medical professionals, and high-ranking officials for further research as the tools that can develop would help to objectively assess injury-related deficits that are mostly missed by the regularly used physical tests. If proven useful, this comprehensive tool can both make insurance claim and discharge policies better suited for all involved as well as improve the quality of life of patients with TBI. For example, drivers who sustain a TBI, could be required to take comprehensive tests such as those presented here, before being allowed to return to work.

Data acquisition will continue to include a large cohort for statistical analysis and to research the three TBI classes and the related specific deficits and appropriate tests. Of these, mild TBI needs particular focus as it tends to be ignored or misdiagnosed, covers 90% of TBI cases presenting to hospital (6), and its symptoms are not usually regarded as serious, even when patients and their families raise credible concerns.

The project will be expanded to include more subjects, to collect a statistically validated large dataset, and to generalize the results to different populations, hospital settings, and LMICs. Other tasks, such as mini-Mental State Exam (MMSE), true/false sentences, and attention studies using disengage tasks such as anti-saccades, etc., will also be included.

Study limitations

The study presents promising evidence that the employed diagnostic tests could serve as practical assessment tools for

Traumatic Brain Injury (TBI) in Low- and Middle-Income Countries (LMICs). Nonetheless, the study confronts several inherent limitations that temper the conclusiveness of its findings. These include a limited participant pool, gender imbalances, and an uneven representation of TBI severity levels.

Furthermore, the study's environment faced logistical challenges, with many hospitals experiencing shortages of basic facilities such as rooms, desks, and even chairs—often leading to medical staff overseeing the procedures while standing. In designing the tests for such constrained settings, there was minimal regulation of external variables like hospital staff interruptions or ambient noise.

Acknowledging the likelihood of participants' unfamiliarity with paper-based and computerized tests, we took extensive measures to provide clear instructions. Testing commenced only after ensuring participants' comprehension and ability to engage fully with the test materials.

In terms of assessment tools, although the Glasgow Coma Scale (GCS) is a recognized predictor of TBI outcomes, it, along with the Glasgow Outcome Scale (GOS) and the extended version (GOS-E), was not used in this study to gauge progress for several reasons. Primarily, the operational context in Ethiopia does not support regular patient follow-ups or standardized treatments for TBI outside of necessary surgical interventions. This means that treatment outcomes depend heavily on individual circumstances. Additionally, the use of GOS and GOS-E is not widespread due to the absence of national treatment standards and a shortage of professionals trained to administer these examinations.

Further research with inclusion of a large cohort and additional tools is necessary to work around these limitations and establish tools and best practices.

Conclusion

Our main findings demonstrate that a simple paper and computer test, implemented by one experimenter can provide useful results to the clinician in assessing several TBI-injury-related deficits in resource-limited settings such as in LMICs. Other findings include: subject demographic data such as education level, which can have significant effects on test performance; alcohol consumption and the possibility of being exposed to TBI incidences. These facts call for collaborative efforts to change the circumstances and allow improved measures to combat the problems. More data with a large sample size is required to appreciate the accuracy of the combined testes in identifying post-TBI deficits. The decision to classify a patient as belonging to one of the TBI categories or as 'control' has great implications and has to be studied carefully. Because medical tests are evaluated for specificity and sensitivity, the need for large data set is critical to ensure that these and other parameters could be estimated with great confidence.

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/s.

Ethics Statement

The studies involving humans were approved by Black Lion Specialized Hospital, Department of Neurosurgery, Addis Ababa, Ethiopia Neurosurgery Unit, College of Health Science. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MS: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. TL: Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition. AA: Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. AT: Writing – review & editing, Supervision, Resources, Project administration, Investigation. YA: Writing – review & editing, Supervision, Resources, Project administration, Investigation. PT: Writing – review & editing, Resources, Project administration, Supervision, Investigation. AK: Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. PH: Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. AB: Writing – review & editing, Supervision, Resources, Project administration, Investigation. DY: Writing – review & editing, Supervision, Resources, Project administration, Investigation. GH: Data curation, Conceptualization, Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was sponsored by the National Institute for Health Research (NIHR) Health Research Group on Neurotrauma (commissioned by the NIHR using Official Development Assistance funding, project 16/137/105).

Acknowledgments

We want to thank all staff and National Institute for Health Research (NIHR) Global Health Research Group members on Neurotrauma, especially Natalia Budohoska, for her unlimited support and commitment to this project. Our heartfelt gratitude goes to our site partner Nasrin Abdulsattar, without whose dedication and assistance, none of this work would be possible. We deeply thank Glen Duncan, whom we sadly lost recently, for designing and making our custom keyboard. We thank all hospitals and their staff for all support, from IRB approval to daily assistance with data gathering. We want to acknowledge Temesgen Beyene, Biruk Getachew, Ayalew Zewdie, Mulualem Wondafrash, Bethelhem Yesehak, Moti Belay, Mekdes, Salahadin, Abera, Gemechu, Eyerusalem Bergene, and

Simbo Mitiku and staff and nurses including Afrah and Amira. Goldberg's precious time spent on detailed editing, proofreading repeatedly and constructive criticism of the manuscript made for a tremendous improvement. Our gratitude also goes to Glenn Wolther and Nicholas Foley for the manuscript editing support.

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.2024.1397625/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 26 July 2024
DOI 10.3389/fneur.2024.1382696

OPEN ACCESS

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RECEIVED 06 February 2024
ACCEPTED 08 July 2024
PUBLISHED 26 July 2024

CITATION
Wang J, Wu Z, Shi S, Ren J and Ren X (2024) Nurse-led care versus neurologist-led care for long-term outcomes of patients who underwent craniotomy in traumatic brain injuries: an efficacy analysis.
Front. Neurol. 15:1382696.
doi: 10.3389/fneur.2024.1382696

Nurse-led care versus neurologist-led care for long-term outcomes of patients who underwent craniotomy in traumatic brain injuries: an efficacy analysis

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Background: After craniotomy, patients require rehabilitation efforts for the recovery process, and neurologists are mostly engaged for that (in the management of post-craniotomy complications). However, neurologists are not always available for care after neurosurgery during follow-up (situation of our institute). The objectives of the study were to compare the effects of two different types of care (nurse-led and neurologist-led) on various long-term outcomes in patients who have undergone craniotomy due to traumatic brain injuries.

Methods: Electronic medical records of patients (aged ≥18 years) who underwent craniotomy for traumatic brain injuries and their caregivers were extracted and retrospectively reviewed. Patients received nurse-led care (NL cohort, $n = 109$) or neurologist-led care (GL cohort, $n = 121$) for 6 months after craniotomy.

Results: Before the nurse-or neurologist-led care (BC), all patients had activities of daily living (ADL) ≤ 11, ≤ 50 quality of life (QoL), and 69% of patients had definitive anxiety, 87% of patients had definitive depression, and all caregivers had Zarit Burden interview scores ≥50. Nurse-led post-surgical care was associated with improved ADL and QoL, relieved anxiety and depression of patients, relieved the burden on caregivers, and the higher overall satisfaction of patients and their caregivers after 6-months of care (AC) as compared to their BC condition ($p < 0.05$) and also compared to those of patients in the GL cohort under AC condition ($p < 0.01$). Patients in the GL cohort reported pressure sores ($p = 0.0211$) and dizziness [15 (12%) vs. 5 (5%)] after craniotomy during follow-up than those in the NL cohort.

Conclusion: ADL, QoL, and psychological conditions of patients who undergo craniotomy for traumatic brain injuries must be improved and the burdens of their caregivers must be relived. Not only is the care provided by nursing staff equivalent to that offered by neurologists, but in some aspects, it is superior for patients who have undergone craniotomy for traumatic brain injuries and their caregivers during follow-up.

KEYWORDS

anxiety, burden on caregivers, craniotomy, cognitive conditions, daily living activity, depression, nurse, neurologist

Introduction

China has a higher number of patients with traumatic brain injuries than most other countries (1). Traumatic brain injury is a major condition that requires several healthcare professionals to provide care in the trauma department (2). In addition, prehospital facilities are insufficient for Chinese emergency care (3). Craniotomy is performed to control intracranial pressure in patients with severe traumatic brain injuries (4). In addition to general postoperative adverse effects (e.g., nausea, vomiting, dizziness), coma, paralysis, mental disabilities, and personality changes are generally reported threats to traumatic brain injuries after craniotomy (2, 5). Craniotomy places patients with traumatic brain injuries at risk of many serious complications, which may affect the outcomes of surgery (6).

Nursing interventions are crucial after neurosurgery and related to patient safety (7). After craniotomy, if nursing care is not sufficiently provided to the patients and the disease conditions of patients are not identified properly and timeously, the possible treatment would be affected, possibly resulting in cognitive impairment or death (8). Improper nursing poses a serious threat after craniotomy in patients with traumatic brain injuries (9). After craniotomy, patients require rehabilitation efforts for the recovery process (10) and neurologists are mostly engaged in the management of post-craniotomy complications (11). However, neurologists are not always available for care after neurosurgery during follow-up (situation of our institute). In addition, in COVID-19 pandemic surgical disciplines have faced serious issues including patients who required surgical care and postoperative follow-up care (12). An important issue is covered as health systems are facing a dire shortage of staff throughout the world. This deserves further scrutiny as to which extent process management can be improved. The findings indicate that the interpersonal skills and communication style of nurses may be more appreciated by patients and caregivers (13). Excellent patient outcomes and high patient satisfaction are two main pillars of the high-value medical care for neurosurgical care of patients (14). In many places, notably the US, post-operative care is typically performed by neurosurgeons with neurologists rarely contributing long-term. Additionally, long-term care varies vastly between settings, largely dependent on infrastructure for patients with a variety of neurodegenerative diseases.

The aim of the retrospective study is to compare the effects of two different types of care (nurse-led and neurologist-led) on various the long-term outcomes (daily living activities (ADL), quality of life (QoL), depression, and anxiety of patients and burden of their caregivers) in patients who have undergone craniotomy due to traumatic brain injuries.

Abbreviations: NL cohort, Patients received nurse-led care after craniotomy for 6 months in follow-up plus regular treatment; GL cohort, Patients received neurologist-led care after craniotomy for 6 months in follow-up plus regular treatment; ADL, Activities of daily living; QoL, Quality of life; SD, Standard deviation; BC, Before any professional (nurse or neurologist)-led care; AC, After 6-months of any professional (nurse or neurologist)-led care; Q1, First Quartile; Q3, Third Quartile; χ^2-test, Chi-square test; GCS, Glasgow Coma Scale.

Materials and methods

Inclusion criteria

Patients (aged ≥18 years) who underwent craniotomy for traumatic brain injuries were included in the study. Patient underwent decompressive hemicraniectomy, or craniotomy with cranial flap repositioning, or both.

Exclusion criteria

Patients with incomplete details were excluded from the study.

Cohort

A total of 109 patients received nurse-led care after craniotomy for 6 months (NL cohort). A total of 121 patients received neurologist-led care for 6 months after craniotomy (GL cohort). In addition to care, all patients received regular treatment prescribed by a consulting neurosurgeon.

Professional-led post-surgical care

Neurologist-led follow-up care

Every day a follow-up visits made in ward by neurologist. In the GL cohort medical follow-up is provided by the neurologist alone, and/or by the neurologist assisted by a neurosurgeon and by a physical medicine physician. Neurologist-led care include usual hospital care (counseling of patients and their caregivers regarding threats and adverse effects of surgeries and injuries) and follow-up of patients (routine check-up). During hospital stay minimum 5 min/day provided to patients by neurologists.

Nurse-led follow-up care

Every day at least two follow-up visits made in ward by staff nurse. In NL cohort medical follow-up is provided by staff nurse oneself. Nurses are minimum postgraduate in nursing care and have minimum 3 years of experiences. Nursing-led care include counseling and education of patients and their caregivers regarding threats and adverse effects of surgeries and injuries. During hospital stay minimum 10 min/day provided to patients by nurses.

After discharge from the hospital, follow-up visits, and telephone consultations with caregivers, and the patients received care from nurses or neurologists. There were no restrictions on telephone consultations with nurses or neurologists for the patients and their caregivers. During the follow-up visit, patients and their caregivers were provided care, counselling, and related instructions for half an hour by a nurse or neurologist. The selection of nurse-led care and neurologist-led care for patients is based on availabilities of professionals in the institutes (in our institutes neurologists are in

short to provide follow-up care). There was no crossover between nurse- and neurologist-led aftercare.

Outcome measures

Glasgow coma scale (GCS)

GCS score was evaluated before craniotomy. GCS scores were between 3 and 15, with 3 being the worst and 15 being good (15).

Activities of daily living

ADL was evaluated for six basic activities: toileting, bathing, dressing, eating, moving, and continence of defecation. Each item is scored from 1 to 3 (1 = complete dependence, 2 = partial dependence, and 3 = complete independence). The total score is 18. The higher the score, the higher the ADL (16).

Quality of life

Physical, emotional, and social functions; somatic pain; general health status; energy; and mental health were used to evaluate QoL. The total score ranged from 0 to 100. The higher the score, the higher the QoL (17).

The hospital anxiety and depression scale

Seven items were evaluated using the Hospital Anxiety and Depression Scale. Each item has a score ranging from 1 to 3. The total scores for anxiety and depression were 21. The higher the score, the higher the anxiety and depression. A score of >7 was considered anxiety and depression, and a score of >11 was considered definitive anxiety and definitive depression (18).

Zarit Burden interview

Questionnaires were administered to caregivers to evaluate their psychological burden due to the patient's condition. It consists of a total of 22 items, and each item is rated on a 0 to 4 scale. The total score was 88, with a higher score indicating a higher burden on caregivers (19).

ADL, QoL, Hospital Anxiety and Depression Scale, and Zarit Burden interview were performed after craniotomy before any professional-led care (nurse-led care or neurologist-led care, BC) and after 6-months of any professional-led care (nurse-led care or neurologist-led care, AC).

Adverse effects

During the 6-months of any professional-led care, any adverse effects due to surgery and/or treatments were noticed and analyzed.

Overall satisfaction score

The institute has a print format to evaluate satisfaction. This included emergency care, pre-surgery counseling, surgery, and professional-led post-surgical care. Each item had a score of 0, 1, 2, 3, and 4. 0, completely dissatisfied; 1, dissatisfied; 2, partially satisfied; 3, satisfied; 4, completely satisfied. The total score is 16. The higher the score, the higher the overall satisfaction of patients and caregivers. The overall satisfaction score was evaluated after professional-led postsurgical care for 6 months.

Statistical analysis

InStat 3.01 (GraphPad Software Inc., San Diego, CA, United States) was used for the statistical analysis. Categorical, continuous normal, and continuous non-normal variables are presented as frequencies with percentages in parentheses, mean ± standard deviation (SD), and medians with Q3–Q1 in parentheses, respectively. All results were considered significant if the p-value was less than 0.05. The Kolmogorov–Smirnov method was adopted to check the normality of continuous variables. If at least one column failed in the normality test with $p < 0.05$, a nonparametric test (Mann–Whitney test or Kruskal-Wallis' test) was performed; otherwise, parametric tests (paired t-test or unpaired t-test) were performed for continuous variables. Fisher's exact test or chi-square test (χ^2-test) was used for the statistical analysis of categorical variables. Dunn's multiple comparison test was used for *post hoc* analysis. The Quartile Calculator[1] was used to calculate the Q3 (third quartile) and Q1 (first quartile) values. All results were considered significant if the p-value was less than 0.05.

Results

Study population

For retrospective study electronic medical records of patients were searched to extract data. From January 18, 2019, to February 20, 2023, 245 patients (age ≥ 18 years) underwent craniotomy for traumatic brain injuries at the Shanxi Bethune Hospital, Taiyuan, Shanxi, China and the referring institutes. Data from 15 patients were incomplete in hospital records. Therefore, these patients were excluded from this study. ADL, QoL, the Hospital Anxiety and Depression Scale of patients, Zarit Burden interview of caregivers, and the overall satisfaction score of patients and caregivers for a total of 230 patients and their caregivers were included in the study. The flowchart of the study is shown in Figure 1.

Demographic and clinical conditions

The number of male patients was higher than that of female patients. Most patients had motor vehicle accidents due to traumatic brain injuries. All patients had a GCS score < 10 before the operation.

1 https://www.calculatorsoup.com/calculators/statistics/quartile-calculator.php

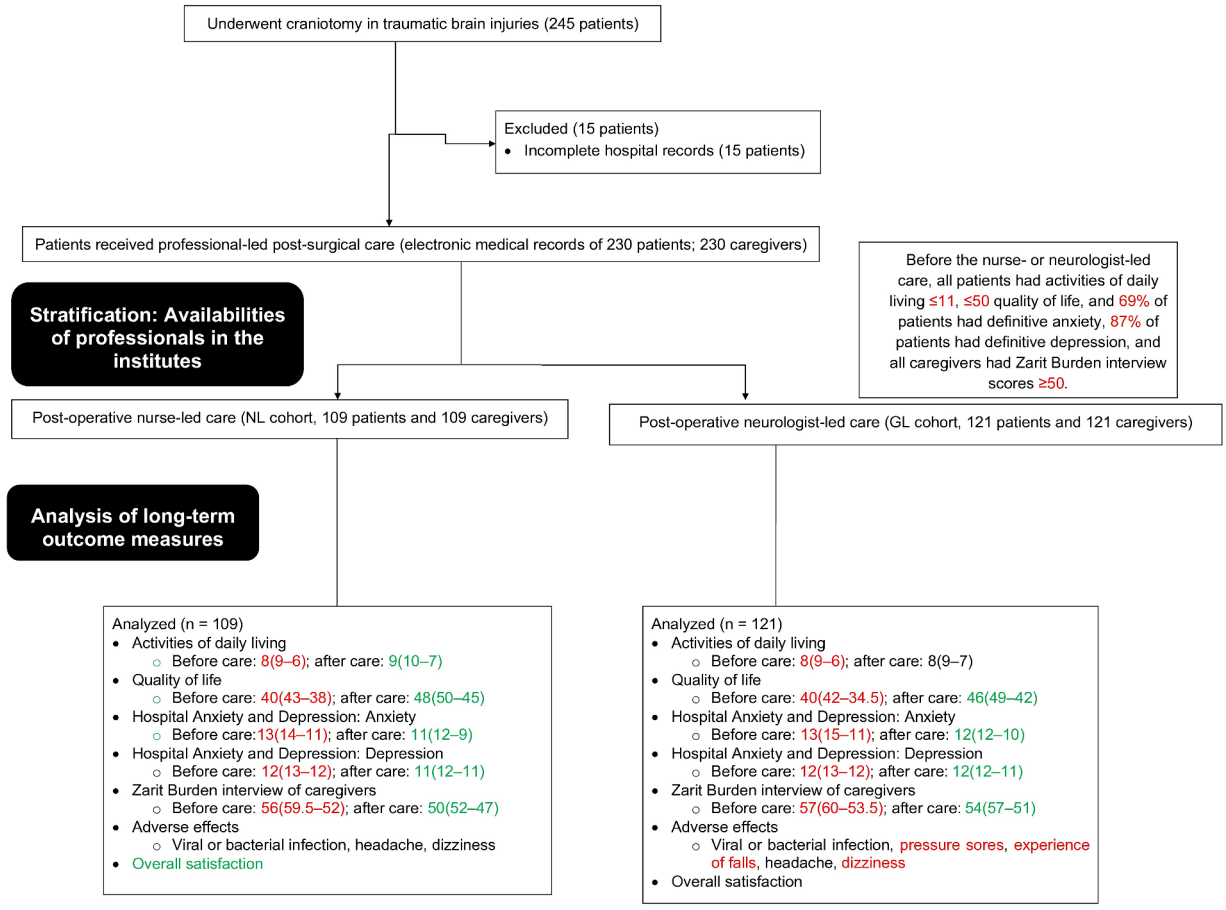

FIGURE 1
The study flow chart. Red color indicates worse results. Green color indicates favorable results. Black color indicates not favorable but not worse results.

Most of the patients underwent surgery on the dominant side. At BC, all patients had an ADL of 11 or fewer, all patients had a QoL of 50 or less, and most of them had definitive anxiety (69%) and depression (87%). Age, sex, reason for traumatic brain injuries, Glasgow Coma Scale score before the operation, surgery side, ADL, QoL, anxiety, and depression of patients were statistically similar between cohorts at BC ($p > 0.05$, Table 1).

All caregivers had Zarit Burden Interview scores of 50 or more at the BC. One patient had a caregiver. Most of the caregivers were spouses. The details of comorbidities of caregivers were not available in the hospital records. Age, sex, education, and Zarit Burden interview scores of caregivers were statistically the same between both cohorts ($p > 0.05$, Table 2).

Outcome measures

Nurse-led post-surgical care was associated with improved ADL of patients with AC condition as compared to their BC condition and also compared to those of the GL cohort in the AC condition. Neurologist-led care was not successful in improving ADL at AC condition compared with their BC condition. Nurse-led care and neurologist-led care were associated with improved QoL, relieved anxiety and depression in patients, and relieved the burden on caregivers of patients at AC condition compared to their BC conditions. In addition, patients in the NL cohort had a better QoL and less anxiety than those in the GL cohort in the AC condition. Caregivers of patients in the NL cohort had fewer burdens than those of caregivers of patients in the GL cohort in the AC condition. The overall satisfaction scores of patients and their caregivers were higher for nurses than that scores for neurologists. The details of the outcome measure of patients and their caregivers after craniotomy for traumatic brain injuries before and after professional-led post-surgical care are presented in Table 3.

Anxiety and depression

Nurse-led care and neurologist-led care both successfully decreased anxiety and depression from definite anxiety (score > 11) to moderate anxiety (score 8–11) in the AC condition compared with their BC conditions. In addition, nurse-led care was more successful in decreasing the anxiety of patients with definite anxiety (score > 11) to moderate anxiety (score 8–11) in the AC condition than those did by neurologist-led care. Nurse-led care or neurologist-led care failed to complete reduce anxiety or depression in patients (score ≤ 7) at the AC condition. The details of the hospital anxiety and depression scales are presented in Table 4.

Adverse effects

None of the patients died during the study. Headache was commonly reported in patients in both cohorts. Pressure sores, dizziness, and experience of falls were reported to be higher in patients in the GL cohort than in those in the NL cohort. The total numbers of adverse events and adverse effects per patient were higher in patients in the GL cohort than those in the NL cohort. The details of adverse effects during the six months of any professional-led care and follow-up period (extra six months) are reported in Table 5.

Discussion

At BC condition, all patients had ≤11 ADL and ≤50 QoL, and most patients had definitive anxiety and depression. In addition, at BC condition all caregivers of patients had Zarit Burden interview scores ≥50. After craniotomy for traumatic brain injuries, the patients had worse ADL, QoL, anxiety, and depression. The outcome results of the patients after craniotomy for traumatic brain injuries are consistent with those of a case–control study (9), a propensity matching study (2), an observational study (17), and a pilot study (7). ADL and QoL of patients after craniotomy for traumatic brain injuries must

TABLE 1 Demographic and clinical conditions of patients after craniotomy for traumatic brain injuries before professional-led post-surgical care.

Parameters		Cohorts		Comparisons between cohorts			
		NL	GL				
Professional for post-surgical care		Nurse	Neurologist				
Numbers of patients		109	121	*p*-value	df	Test value	95% CI
Age (years)		36 (44.5–31)	41 (46–33)	0.1675 (Mann–Whitney test)	N/A	5898.5	N/A
Gender	Male	75 (69)	70 (58)	0.1136 (χ^2-test with Yates correction)	1	2.503	0.9539 to 1.753
	Female	34 (31)	51 (42)				
Reason for traumatic brain injuries							
Motor vehicle accident		89 (82)	95 (78)	0.8721 (χ^2-test for independence)	3	0.7048	N/A
Fall		8 (7)	12 (10)				
War or training		7 (6)	7 (6)				
Violence		5 (5)	7 (6)				
@Glasgow Coma Scale before the operation		7 (8–7)	7 (8–7)	0.4929 (Mann–Whitney test)	N/A	6252.5	N/A
Surgery side							
Dominant side		65 (60)	65 (54)	0.4788 (χ^2-test for independence)	2	1.473	N/A
Non-dominant side		35 (32)	48 (40)				
Bilateral		9 (8)	8 (6)				
ADL		8 (9–6)	8 (9–6)	0.8681 (Mann–Whitney test)	N/A	6510.5	N/A
QoL		40 (43–38)	40 (42–34.5)	0.3317 (Mann–Whitney test)	N/A	6,105	N/A
Anxiety scale	≤7	0 (0)	0 (0)	0.8075 (χ^2-test with Yates correction)	1	0.0593	0.7935 to 1.414
	8–11	35 (32)	36 (30)				
	>11	74 (68)	85 (70)				
	Value	13 (14–11)	13 (15–11)	0.2283 (Mann–Whitney test)	N/A	5931.5	N/A
Depression scale	≤7	0 (0)	0 (0)	0.2291 (Mann–Whitney test)	N/A	5993.5	N/A
	8–11	10 (9)	21 (17)				
	>11	99 (91)	100 (83)				
	Value	12 (13–12)	12 (13–12)				

Categorical and continuous normal or ordinal variables are depicted as frequencies with percentages and medians with Q3–Q1 in parenthesis, respectively.
All results are considered significant if the *p*-value is less than 0.05.
CI: Confidence interval (using the approximation of Katz. for categorical variables), N/A: Not applicable, df: Degree of freedom.
Test value (Mann–Whitney U-statistics for Mann–Whitney test, χ^2-value for χ^2-test).
@Values was between 3 and 15, 3 being the worst and 15 being good.
ADL: Activities of daily living (total score is 18. Higher the score, the higher is ADL).
QoL: Quality of life (the total score range was from 0 to 100. The higher the score higher is QoL).
Anxiety scale (total score was 21. The higher the score higher is anxiety).
Depression scale (total score was 21. The higher the score higher is depression).
≤ 7: No anxiety/ depression.
8–11: moderate anxiety/ depression.
11 >: definite anxiety/depression.

TABLE 2 Available demographic and clinical conditions of caregivers of patients after craniotomy for traumatic brain injuries before professional-led post-surgical care of patients.

Parameters		Cohorts		Comparisons between cohorts			
		NL	GL				
Professional for post-surgical care of patients		Nurse	Neurologist				
Numbers of caregivers		109	121	*p*-value	df	Test value	95% CI
Age (years)		36 (45–31)	41 (45–31)	0.5791 (Mann–Whitney test)	N/A	6314.5	N/A
Gender	Male	59 (54)	60 (50)	0.5781 (χ^2-test with Yates correction)	1	0.3093	0.8369 to 1.448
	Female	50 (46)	61 (50)				
Education	Primitive	10 (9)	12 (10)	0.9776 (χ^2-test for independence)	3	0.1998	N/A
	Below higher secondary	63 (58)	72 (59)				
	Above higher secondary but not graduate	25 (23)	25 (21)				
	Graduate or above or professional course	11 (10)	12 (10)				
Zarit Burden interview score		56 (59.5–52)	57 (60–53.5)	0.3194 (Mann–Whitney test)	N/A	6092.5	N/A

Categorical and continuous ordinal variables are depicted as frequencies with percentages in parenthesis and medians with Q3–Q1 in parenthesis, respectively.
All results are considered significant if the *p*-value is less than 0.05.
CI: Confidence interval (using the approximation of Katz. for categorical variables), N/A: Not applicable, df: Degree of freedom.
Test value (Mann–Whitney U-statistics for Mann–Whitney test, χ^2-value for χ^2-test).
Zarit Burden interview score (Total score is 88, higher score indicates higher burden on).

TABLE 3 The outcome measures of patients and their caregivers after craniotomy for traumatic brain injuries before and after professional-led post-surgical care.

Parameters	Cohorts								Comparisons between cohorts at AC	
	NL				GL					
Professional for post-surgical care	Nurse				Neurologist					
Numbers of patients	109	109	Comparisons between BC and AC		121	121	Comparisons between BC and AC			
Numbers of caregivers	109	109			121	121				
Level	BC	AC	*p*-value	Kruskal-Wallis' test-statistics	BC	AC	*p*-value	Kruskal-Wallis' test-statistics	*p*-value	Kruskal-Wallis' test-statistics
ADL of patients	8 (9–6)	9 (10–7)	<0.001	26.551	8 (9–6)	8 (9–7)	0.1304	4.074	<0.01	21.312
QoL of patients	40 (43–38)	48 (50–45)	<0.001	140.42	40 (42–34.5)	46 (49–42)	<0.001	96.504	<0.05	121.13
Anxiety scale of patients	13 (14–11)	11 (12–9)	<0.001	83.463	13 (15–11)	12 (12–10)	<0.001	39.052	<0.01	61.378
Depression scale of patients	12 (13–12)	11 (12–11)	<0.001	92.027	12 (13–12)	12 (12–11)	<0.001	70.443	0.1118	5,802
Zarit Burden interview score of caregivers	56 (59.5–52)	50 (52–47)	<0.001	110.76	57 (60–53.5)	54 (57–51)	<0.001	21.524	<0.001	86.834
Overall satisfaction score of patients and their caregivers	N/A	11 (12–10)	N/A	N/A	N/A	9 (10–9)	N/A	N/A	<0.0001	4,354

Variables are depicted as medians with Q3–Q1 in parenthesis.
Mann–Whitney test or Kruskal-Wallis' test was used for statistical analysis. Dunn's Multiple Comparisons test was used for *post hoc* analysis.
All results are considered significant if the *p*-value is less than 0.05.
BC: Before any professional (nurse or neurologist)-led care, AC: After 6 months of any professional (nurse or neurologist)-led care, N/A: Not applicable.
ADL: Activities of daily living (Total score is 18. Higher the score, the higher is ADL).
QoL: Quality of life (The total score range was from 0 to 100. The higher the score higher is QoL).
Anxiety scale (Total score was 21. The higher the score higher is anxiety).
Depression scale (Total score was 21. The higher the score higher is depression).
Zarit Burden interview score (Total score is 88, a higher score indicates a higher burden on caregivers).
Overall satisfaction score (Total score is 16. The higher the score, the higher the overall satisfaction of patients and caregivers).

TABLE 4 The details of the hospital anxiety and depression scales.

Scale	Cohorts												Comparisons between cohorts			
	NL						GL									
Professional for post-surgical care	Nurse						Neurologist									
Level	BC	AC	*p*-value	df	Test value	95% CI	BC	AC	*p*-value	df	Test value	95% CI	*p*-value	df	Test value	95% CI
Numbers of patients	109	109					121	121								
Anxiety																
≤7	0 (0)	1 (1)	<0.0001 (χ^2-test for independence)	2	21.713	N/A	0 (0)	0 (0)	0.045 (χ^2-test with Yates correction)	1	4.018	0.5553 to 0.9892	0.0059 (χ^2-test for independence)	2	10.251	N/A
8–11	35 (32)	68 (62)					36 (30)	52 (43)								
>11	74 (68)	40 (37)					85 (70)	69 (57)								
Depression																
≤7	0 (0)	0 (0)	<0.0001 (Fisher's exact test)	N/A	0.2228	0.1243 to 0.3995	0 (0)	0 (0)	<0.0001(χ^2-test with Yates correction)	1	0.45	0.3062 to 0.6613	0.0828 (Fisher's exact test)	N/A	0.6484	0.3820 to 1.101
8–11	10 (9)	58 (53)					21 (17)	56 (46)								
>11	99 (91)	51 (47)					100 (83)	65 (54)								

Variables are depicted as frequencies with percentages in parentheses.
All results are considered significant if the *p*-value is less than 0.05.
≤ 7: No anxiety/ depression.
8–11: moderate anxiety/ depression.
11 >: definite anxiety/depression.
Test value (χ^2-value for χ^2-test, relative risk for Fisher's exact test).
BC: Before any professional (nurse or neurologist)-led care, AC: After 6-months of any professional (nurse or neurologist)-led care, df: Degree of freedom, CI: Confidence interval (using the approximation of Katz.), N/A: Not applicable.

10.3389/fneur.2024.1382696

TABLE 5 The details of adverse effects during the six months of any professional-led care and follow-up period.

Effect	Cohorts		Comparisons between cohorts			
	NL	GL				
Professional for post-surgical care	Nurse	Neurologist				
Numbers of patients	109	121	*p*-value	df	Test value	95% CI
Viral or bacterial infection	3 (3)	4 (3)	0.9999 (Fisher's exact test)	N/A	0.9016	0.3790 to 2.145
Pressure sores	2 (2)	11 (9)*	0.0211 (Fisher's exact test)	N/A	0.312	0.08655 to 1.125
Rebleeding	1 (1)	2 (2)	0.9999 (Fisher's exact test)	N/A	0.7006	0.1405 to 3.493
Central hyperthermia	1 (1)	1 (1)	0.9999 (Fisher's exact test)	N/A	1.056	0.2621 to 4.251
Experience of falls	3 (3)	10 (8)	0.0889 (Fisher's exact test)	N/A	0.4724	0.1734 to 1.287
Hypertension	2 (2)	4 (3)	0.686 (Fisher's exact test)	N/A	0.6978	0.2231 to 2.182
Nausea	3 (3)	4 (3)	0.9999 (Fisher's exact test)	N/A	0.9016	0.3790 to 2.145
Headache	15 (14)	21 (17)	0.4737 (Fisher's exact test)	N/A	0.8599	0.5690 to 1.3
Dizziness	5 (5)	15 (12)	0.0585 (Fisher's exact test)	N/A	0.5048	0.2334 to 1.092
Total numbers of adverse events	30	57*	0.0035 (χ^2-test with Yates correction)	1	8.538	0.4509 to 0.8640
Adverse effect/ patient	0.28	0.47	N/A	N/A	N/A	N/A

Variables are depicted as frequencies with percentages in parentheses.
Patients had one or more adverse effect(s).
All results are considered significant if the *p*-value is less than 0.05.
CI: Confidence interval (using the approximation of Katz), N/A: Not applicable, df: Degree of freedom.
Test value (relative risk for Fisher's exact test, χ^2-value for χ^2-test).
*Significant adverse effects were reported in patients of the GL cohort than those of the NL cohort.
Adverse effects after craniotomy for traumatic brain injuries before professional-led post-surgical care were not included in the above analysis.

be improved and anxiety and depression of patients after craniotomy for traumatic brain injuries must be relieved. In addition, after craniotomy for traumatic brain injuries, the burden on caregivers of patients must be relieved.

Nurse-led care improved ADL and QoL and relieved anxiety and depression in patients with AC conditions as compared to their BC conditions and those of patients of the GL under AC conditions. The results of the NL cohort were consistent with those of a case–control study (9) and a trial on multiple sclerosis (13). In addition, nurse-led care relieved the burden on caregivers of patients with AC conditions compared to the BC conditions and those of caregivers of patients with the GL cohort under AC conditions. Nurse-led care and neurologist-led care are associated with the improvement of ADL and QoL, relief of anxiety and depression in patients after craniotomy for traumatic brain injuries, and relief of burden on caregivers. Moreover, nurse-led care is superior to neurologist-led care in the follow-up of patients after craniotomy for traumatic brain injuries, regarding the improvement of ADL, QoL, and psychological conditions of patients and burdens of their caregivers. Frequent visits of nurses to patients and caregivers than those of neurologists are the reasons for these results.

Patients in the GL cohort reported pressure sores, dizziness, experience of falls, higher numbers of total adverse effects, and higher adverse effects per patient during six months of care and a follow-up period than those in the NL cohort. Neurologists are not always available for care after neurosurgery during follow-up to provide mobility to patients (situation of our institute). This would lead to a high risk of pressure sores, falls while walking, and dizziness in patients of the GL cohorts (20). Nurse-led care during follow-up decreases adverse effects after craniotomy for traumatic brain injuries compared with neurologist-led follow-up care.

The overall satisfaction scores of patients and their caregivers were higher for nurses than for neurologists. Compared with neurologists, nurses provide more time to patients and their caregivers. The results of the overall satisfaction scores of patients and their caregivers of the current study are consistent with a trial on multiple sclerosis (13). In addition, nurses have better communication skills and require fewer waiting times than neurologists (21). Nurses provide advanced skills to various complex medical conditions, with potential to enhance the health, cognitive functioning, and quality of life (22). Nurses can also develop interpersonal relationships. This would increase the satisfaction of the patients and caregivers.

These interpretations of the results cannot be extrapolated as an indication of the best treatment for the recovery of these patients, which must include multidisciplinary management, where in addition to neurological doctors and nurses, many other professionals participate, such as neuropsychologists, rehabilitators, physiotherapists, speech therapists, etc. Each of them will contribute in each area to try to maximize the possibilities of functional recovery. However, it is obvious that the local context may prevent having all the resources available and that these are optimized and, in this situation, directed in the best possible way.

Both nurse-led and neurologist-led care were unsuccessful in completely removing anxiety or depression in patients (score ≤ 7) at AC. This suggests that additional treatment interventions may be needed to address these (anxiety and depression) issues of patients.

In the current study research outcome measures such as ADL, QoL, the Hospital Anxiety and Depression Scale of patients, and Zarit Burden interview of caregivers, as well as the overall satisfaction score of patients and caregivers were evaluated. The objectives of study were to evaluate long-term outcome measures of patients who have

TABLE 6 Comparative studies on professional-led post-surgical care after craniotomy (neurosurgeries) for traumatic brain injuries.

Study	Published year	Ethnicity	Study population	Sample size (N; patients)	Age range
Pilot study, Johnson et al. (7)	2021	North America	Patients with indwelling shunts	8 patients	14–18 years
Case–control study, Jing et al. (9)	2022	Chinese	Patients undergoing neurosurgery	120 patients	18–75 years
Scoping review, Sveen et al. (10)	2022	World population	Patients faced traumatic brain injury	425 articles	Adult (range is not specified)
Randomized trial, Smyth et al. (13)	2022	Canadian	People with Multiple Sclerosis	220 patients	47.47 ± 11.02
Retrospective study, Young et al. (14)	2020	North America	Patients admitted to the neurosciences intensive care unit following a craniotomy	314 patients	40–70 years
Observational study, Zhao and Wang, (17)	2023	Chinese	Patients undergoing craniocerebral injury surgery	105 patients	Adult (range is not specified)
Observational study, Hong et al., (20)	2021	Chinese	Intracerebral hemorrhage patients	72 patients	60–85 years

undergone craniotomy due to traumatic brain injuries. These (ADL, QoL, the Hospital Anxiety and Depression Scale of patients, and Zarit Burden interview of caregivers) are good predictors of long-term outcome measures (2).

The study claims that this article is a retrospective study, and it is well known that retrospective studies look at past data to conclude the present. In the daily work of hospitals, many aspects are not routinely evaluated, such as ADL and Zarit Burden interviews. In general practice, these indicators mentioned in the article are obtained through retrospective research. The possible justification for the same is that in the daily work of our hospital many aspects, such as ADL and Zarit Burden interviews are routinely evaluated.

The compilation of the comparative studies on professional-led post-surgical care after craniotomy (neurosurgeries) for traumatic brain injuries used in the current study for re-iteration of research findings (current research or past researches) is presented in Table 6.

In the study the results obtained in the late care of patients undergoing surgery for a traumatic brain injury are compared depending on whether these cares were provided by neurologists or nursing staff. The reason for raising this dilemma and this analysis seems to be the lack of medical personnel in the area of origin of the study. However, there are few limitations of this study, for example, its retrospective design and lack of randomized trials, with inherent limitations in obtaining information and biases in its analysis. The study has small cohorts which limits generalizability. Future research should consider incorporating more objective measures and providing more detailed information on adverse effects.

Conclusion

The activities of daily living and quality of life of patients after craniotomy for traumatic brain injuries must be improved, and anxiety and depression of patients after craniotomy for traumatic brain injuries must be relieved. Burden of caregivers of patients must be relieved after craniotomy for traumatic brain injuries. Nurse-led care and neurologist-led care are associated with improvement in quality of life, relief of anxiety and depression in patients after craniotomy for traumatic brain injuries, and relief of burden on caregivers of patients. Nurse-led care is superior to neurologist-led care in six months of the follow-up of patients after craniotomy for traumatic brain injuries, regarding the improvement of activities of daily living, quality of life, and psychological conditions of patients and burdens of their caregivers. Nurse-led care during follow-up decreases adverse effects after craniotomy for traumatic brain injuries compared with neurologist-led follow-up care. Patients and their caregivers may have higher satisfaction for nurses than neurologists with follow-up care after craniotomy for traumatic brain injuries. So is the consideration that patients after craniotomy for traumatic brain injuries have of nurse-led care. This study provides additional context and support for the benefits of nurse-led care after craniotomy in traumatic brain injuries.

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 study protocol was designed and approved by the human ethics committee of the Shanxi Bethune Hospital and the Chinese Neurotrauma Scholar Association (Approval number 2019YJ18 dated January 11, 2019). The study follows the laws of China and the v2008 Declarations of the Helsinki. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JW: Conceptualization, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. ZW: Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. SS: Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. JR: Data curation, Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. XR: Conceptualization, Data curation, Formal

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Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by Shanxi Bethune Hospital (No: 2019YJ18).

Acknowledgments

The authors are thankful to the medical and nursing staff of the Shanxi Bethune Hospital, Taiyuan, Shanxi, China.

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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frontiers | Frontiers in Neurology

TYPE Clinical Trial
PUBLISHED 07 August 2024
DOI 10.3389/fneur.2024.1443982

OPEN ACCESS

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RECEIVED 14 June 2024
ACCEPTED 25 July 2024
PUBLISHED 07 August 2024

CITATION
Foresti ML, Garzon E, de Moraes MT, Valeriano RPS, Santiago JP, dos Santos GM, Longo NM, Baise C, Andrade JCQF, Susemihl MA, Leite CdC, Naffah Mazzacoratti MdG, Paiva WS, de Andrade AF, Teixeira MJ and Mello LE (2024) Initial clinical evidence on biperiden as antiepileptogenic after traumatic brain injury—a randomized clinical trial.
Front. Neurol. 15:1443982.
doi: 10.3389/fneur.2024.1443982

Initial clinical evidence on biperiden as antiepileptogenic after traumatic brain injury—a randomized clinical trial

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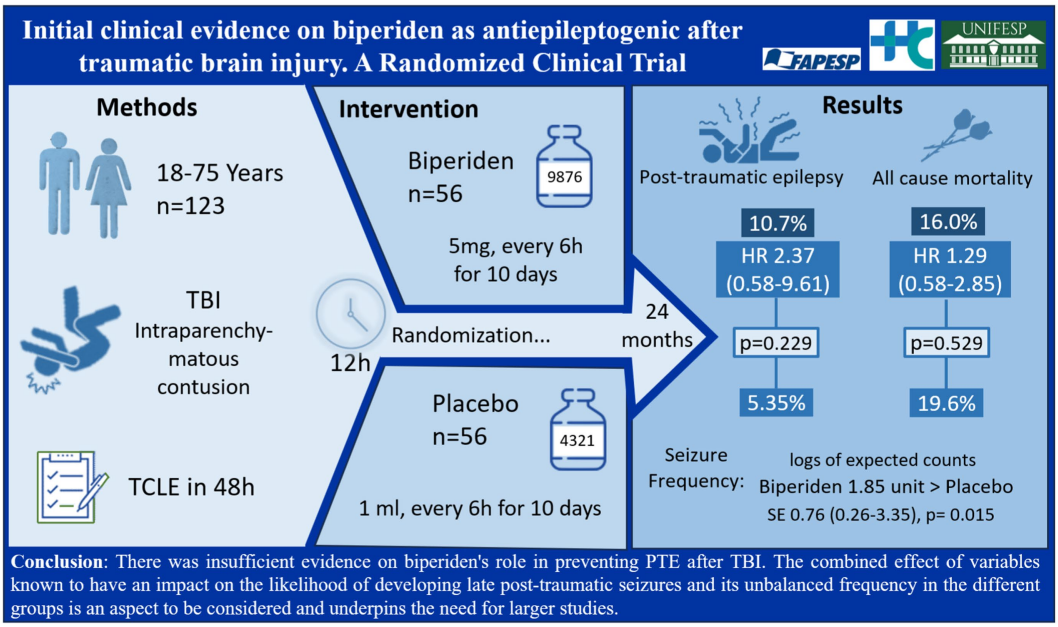
There is currently no efficacious intervention for preventing post-traumatic epilepsy (PTE). Preclinical studies support the potential use of anticholinergics for this condition. The purpose of this study was to evaluate the effects of biperiden as an intervention for preventing PTE. A randomized, double-blinded clinical trial was conducted at HC/FMUSP between 2018–2022. Adults with acute traumatic brain injury (TBI) were randomly assigned to receive biperiden or placebo, for 10 days. The primary outcome was the incidence of PTE while the secondary outcomes included the frequency of seizures, the frequency of any adverse events and mortality after 24 months. The study was powered at a planned enrolment of 132 patients. The trial began in January 2018 and was halted by researchers on March 2020 (and terminated in December 2022) in the face of the global COVID-19 pandemic. Overall, 123 participants were randomized and 112 contributed with data for modified mITT analysis, being that 61 (49.5%) participants completed the 24-month follow-up consult. Data analysis indicated lack of evidence of biperiden for either, the incidence of post-traumatic epilepsy (2.6, 95%CI, 0.65–10.57; p = 0.170) or the mortality rate (1.57, 95%CI, 0.73–3.38; p = 0.248). The frequency of late post-traumatic seizures was higher for biperiden group (2.03, 95%CI = 0.912–3.1597; p <0.001). The present study suggests that there was insufficient evidence regarding the effect of biperiden in preventing PTE after TBI, which underpins the need for larger studies.

Clinical trial registration: ClinicalTrials.gov, identifier: NCT01048138.

KEYWORDS

acute traumatic brain injury, post traumatic epilepsy, seizure, epilepsy, anticholinergic, biperiden



GRAPHICAL ABSTRACT

Introduction

Traumatic brain injury (TBI) has about 27 million new cases globally, resulting in 346 cases per 100,000 population incidence rate, according to the most up-to-date systematic analysis for the Global Burden of Disease (GBD) of TBI (1). One of the major neurological sequelae associated with TBI is post-traumatic epilepsy (PTE), which is characterized by recurrent, unprovoked seizures, starting within months to years after TBI (2). The incidence of PTE has been difficult to define owing to inadequacies in seizure reporting, long-term follow-up and variations in study approaches (2), but it is estimated that affects 2.1, 4.2, 16.7 to 50% of patients with mild, moderate, severe and penetrating TBI (3, 4). PTE impairs neurological recovery after TBI and is independently associated with poor functional outcomes (5).

Despite the available knowledge, there is currently no effective and safe intervention to prevent PTE, and no clinically available medications that have direct actions on the underlying disease process leading to seizures or its progression (6). Indeed, recent terminology recommendations proposed by the International League Against Epilepsy indicate that the pharmacological class that was previously known as antiepileptic drugs, should be named as antiseizure medications (ASM). This change recognizes the fact that ASM are unable to suppress the underlying medical condition, that is epilepsy (7). In fact, only a few antiseizure medications have ever been evaluated for the prevention of PTE in randomized controlled trials (RCTs), and all failed (8). Still, agents that are approved for use in a number of conditions in humans have been successful in affecting disease progression in animal models of epilepsy but have yet to be tested in the clinical setting as antiepileptogenic agents (9). In fact, although the safety profile of repurposed drugs is much better understood than for a new molecule, the availability of studies assessing the second use of an already existing medication, is less than it would be desired.

Original research revealed the potential antiepileptogenic effects of anticholinergic drugs (10). In these studies, drugs that modify neuronal plastic processes, such as anticholinergic agents (e.g., antimuscarinic compounds), have shown the potential to modify the natural course of post-traumatic epilepsy, by decreasing the incidence and intensity of spontaneous epileptic seizures and delaying their appearance in animal models of epilepsy (10). Here, we provided a first assessment of the use of an antimuscarinic compound into real-world use, by investigating whether biperiden, a widely used drug for other pathologies (e.g., Parkinson), in patients after TBI.

In addition to being a routine antiparkinsonian agent with decades of use in millions of patients worldwide (11), there have also been reports on the experimental use of biperiden for the treatment of depression (12, 13). The available evidence indicates its effect on Parkinson's to be associated with modulation of the cholinergic neurons in the striatum (14). In contrast, its potential use as an antidepressant has yet to be understood, despite some suggestions of an effect via BDNF/TrkB signaling (15). For its purported application as an antiepileptogenic or disease-modifying agent, the testing hypothesis revolves around the modulation of plastic phenomena (10).

Therefore, considering that TBI leading to PTE provides the best opportunity for investigating epileptogenesis employing a parallel animal/human research paradigm (16), the primary goal of this clinical study was to present preliminary outcomes from a double-blind, randomized, placebo-controlled study. This study aimed to evaluate the effects, both beneficial and adverse, of administering biperiden to individuals with TBI as a preventive measure against PTE.

Methods

Design and setting

This was a randomized, double-blinded clinical trial, conducted at Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP) in collaboration with Hospital São Paulo,

Universidade Federal de São Paulo, Brazil, between 2018 (31/01/2018) and 2022 (21/12/2022). The study protocol was registered with ClinicalTrials.gov (NCT01048138) available from: https://www.clinicaltrials.gov/study/NCT01048138.

This report followed the recommendation of the Consolidated Standards of Reporting Trials (CONSORT) checklist (17).

Ethical aspects

The study protocol was approved by the Local Research Ethics Committee at HC-FMUSP (number 08533513.6.2002.0068) and Unifesp (number 08533513.6.1001.5505). All patients enrolled in the study provided informed consent. Alternatively, inclusion in the study was granted by a legal representative.

Participants

Patients with acute TBI admitted at the emergency care unit (ECU) of the HC-FMUSP, between January 2018 and December 2020 were screened. Screening procedures, including standard computerized tomography (CT) scan evaluation, were performed by the resident neurosurgeon involved in the care of the patient to determine subject eligibility criteria.

Inclusion criteria were age 18–75 years; diagnosis of acute TBI admitted to the emergency unit within 12 h of the trauma, regardless of the accident; brain CT scan with signs of acute intraparenchymatous contusion; signed informed consent (possibly by a relative, within 48 h after inclusion). Exclusion criteria were history of epilepsy or use of anti-seizure medication (ASM); previous history of TBI; previous cerebrovascular accident; malignant neoplasia and other severe comorbidities; neurodegenerative disorders; concomitant use of other anticholinergic medications; pregnancy; presence of any factor that might contraindicate the use of biperiden; current inclusion in another clinical trial. Alcohol intoxication did not lead to exclusion of the subject.

Sample size

In order to detect a reduction in the incidence of PTE from 23% in the placebo group to 5% in the biperiden group, with an alpha risk of 5% and power of 80%, this trial was originally designed to enroll 132 patients, being 57 patients in each treatment arm (placebo and biperiden) and an additional 18 patients to compensate eventual screening failure or follow-up loss. However, recruitment and funding issues, and mainly the SARS-CoV-2 pandemic prompted an adjustment in the study design to stop enrollment at 123 patients.

Randomization, allocation concealment, and blinding

Randomization was performed using random numbers generated by the SPSS statistical package (14.0 for Windows, SPSS Inc), and was done at a 1:1 ratio of placebo and biperiden, in blocks of 6, by an unblinded investigator. Each ampoule was tagged according to the randomly allocated number. Next, tagged ampoules were organized in crescent order and sequentially dispensed by a blinded pharmacist, following the sequential inclusion of participants admitted in the ECU.

Biperiden was presented at an amber ampoule of 1 mL (5 mg/mL; Cinetol, Cristália, Brazil) and had its commercial tag replaced by a numbered tag (following random generated numbers, as already described). Placebo consisted of 1 mL of sterile 0.9% saline solution. Although saline solution had similar color, odor and texture of biperiden, placebo amber ampoule was slightly larger (11.9%) than biperideno ampoules owing to specificities of the production machinery. Except for this, both color and shape of the placebo ampoule, as well as the numbered tag, were identical to the biperiden ampoule. Therefore, care providers (managing physicians and nurses) were partially blinded, given that despite lacking awareness of group assignment, those minimal bottle size differences could be recognized if closely compared. Study medication was stored and dispensed by the hospital pharmacy service to the nurses engaged in the trial, which also kept the records of the distribution of medications used in this clinical trial, to provide drug accountability.

Intervention

Once the patient was enrolled, 1 mL of the study randomized medication, biperiden or placebo, was diluted in 10–50 mL of sterile saline, and intravenous administered by assistant nurses as soon as possible within 12 h after TBI, aiming at modifying the epileptogenic process. The intervention was repeated every 6 h for 10 consecutive days, until completing 40 total doses (10, 18).

Demographic and clinical data of the patients were collected, including the occurrence of acute symptomatic seizures (seizures occurring immediately after TBI until 7 days after trauma). The incidence of already known clinical adverse events for biperiden use and other events were evaluated during the intervention period. Patients were not deprived of any medical treatment, including use of ASM (such as phenytoin, mainly during the acute hospitalization period when presenting with acute symptomatic seizures following TBI), indicated for their case.

For the follow up, clinical evaluation was performed by blinded experienced epileptologists at 1, 3, 6, 12, 18 and 24 months after TBI. At each visit, any adverse events were assessed, and neurologic examination was performed, focusing on the occurrence of unprovoked epileptic seizures, including absence seizures, starting 7 days after TBI, which characterize PTE. Therefore, the PTE diagnosis was defined based on detailed clinical history that was obtained from the patient and family members, guided by experienced epileptologists regarding key points for seizure diagnosis.

It is important to highlight that, unfortunately, due to the restrictive social measurements imposed by the SARS-CoV-2 pandemic in 2020/2021, the in person follow up assessments to verify history of seizure occurrence, and its clinical characteristics in order to classify seizures types, had to be replaced by phone calls, which continued to be performed by the same epileptologists.

Outcomes

Primary outcome was the incidence of PTE. The incidence of PTE was evaluated by identifying spontaneous seizures initiated 7 days after TBI and during the two-year follow-up period. PTE incidence

was compared between placebo and biperiden-treated patients at 24 months.

Secondary outcomes: i. Frequency of seizures. The frequency of seizures was counted starting 7 days after TBI and during the two-year follow-up period. Frequency of seizures was compared between placebo and biperiden-treated patients at 24 months after TBI. ii. Mortality and adverse effects. The incidence of death and adverse effects was counted starting immediately after TBI and continuously, during the intervention period (for the adverse events), or the two-year follow-up period (for mortality). Incidence of death and adverse effects was compared between placebo and biperiden-treated patients at 10 days and 24 months after TBI, respectively.

As part of an exploratory extended study, which results will be reported separately, acute and chronic electroencephalogram (EEG), genetic and behavioral data were also monitored for assessing potential mechanisms by which biperiden might exert its actions on epileptogenesis.

Statistical analysis

For continuous outcomes, means and standard deviation (SD) values are presented. For categorical data, proportions and counts are presented. For an even more precise characterization of study participants, it is presented the features of age and Glasgow Coma Scale on scene (GCSoS) of the accident, as well as on hospital admission (GCSoA), both as continuous data, used at statistical analysis, and as categorized data, which is relevant for clinic interpretation.

Cox regression (Breslow method for ties) was used to assess the difference between groups on the two time-to-event outcomes (PTE and mortality). The assumption of proportional hazards was tested via Schoenfeld residuals. Moreover, given that mortality is a competing risk of PTE incidence, we used the competing-risks regression based on Fine and Gray's proportional subhazards model for the PTE modeling as a sensitivity analysis.

Zero-inflated Poisson regression with robust standard error (19) was used to estimate the effect of the intervention on the seizure frequency (number of post-traumatic seizures), which is the secondary outcome.

The GCSoS was used as an adjustment given that it is described in the literature that GCS can be a predictor of PTE (5, 20) and, therefore, based on a clinical perspective. However, note that both unadjusted and adjusted estimates are reported to give transparency regarding the effects, especially given that the outcomes are time-to-event (21). Due to missing data in GCSoS and to avoid reduction in the power due to missing in covariate GCSoS when running adjusted models, it was used multiple imputations. The following measures were considered in the unrestricted models for the imputation: age, sex, and group randomization. Because all those measures had non-missing values, they were used only as predictors in the unrestricted model. It was imputed ten datasets and the results presented are the pooled estimates. STATA version 14 was used for all the analyses. The statistical significance level adopted was 0.05. Final analyses were performed by a blinded statistician.

Results

A total of 122 adult consecutive patients with TBI meeting the inclusion criteria were recruited from January 2018 to March 2020, when patient's recruitment was suspended due to the social isolation measures imposed by the SARS-CoV-2 pandemic. A single patient was recruited in December 2021, totalizing 123 recruited patients. Of these, 59/123 patients (47.9%) were randomized for the Placebo group and 64/123 patients (52%) were randomized for the Biperiden group (Figure 1). Imbalanced sample sizes can be partially explained by the premature termination of the study. Additionally, we encountered two cases of broken boxes that were discarded, and we continued with the expected sequence of allocation. As already pointed out, with the social restrictions measures implemented as a result of the SARS-CoV-2 pandemic, the monitoring of patients after hospital discharge was interrupted as of March 2020. After a period of reorganization, some clinical follow-ups were carried out through telephone calls, in an attempt to maintain the link between patients and the project team and to monitor the emergence of PTE. Despite being effective, there was a delay in the evaluation of many patients, especially for those completing the follow-up period in 2020/2021 pandemic. A total of 3/123 patients (2.4%) were lost in the follow-up, without completing any visits. A total of 27/123 patients (21.9%) died during the two-year follow-up (placebo $n = 11$, biperiden $n = 16$). In addition, 11/123 (8.9%) patients were excluded or discontinued from the study, mostly for presenting previous epilepsy ($n = 7$), declining participation ($n = 2$) or receiving only a few doses for failing eligibility criteria ($n = 2$), and therefore were not included in the modified mITT analysis. Overall, of the 82/123 (66.6%) remaining participants, a total of 61/123 (49.5%) participants (placebo $n = 33$, biperiden $n = 28$) completed the last study assessment, comprising the 24 months period after TCE (last appointment ranged between 23 and 45 months). Figure 1 shows the flowchart of the trial.

Considering all participants, 22/123 (17.8%) were female with mean (SD) age of 51.7 (20.0) years and 101/123 (82.1%) participants were male, with 42.0 (16.7) years, resulting in 43.7 (17.6) mean (SD) age for the whole sample.

Tables 1, 2 are descriptive statistics for all participants in terms of continuous and categorical measures, respectively. It might be observed that the groups are balanced in terms of demographic and clinical features, including those related to the incidence of ASS. However, it is important to highlight that it was observed some unevenness among groups when considering some clinic aspects relevant for the PTE development, e.g., given the known GCSoS (data available for 85/123 (69.1%) participants), the biperiden group had 35/45 (77.7%) participants with moderate and severe TBI, while the placebo group presented 23/40 (57.5%) participants with this TBI severity. Such distributions are more even if considering the GCSoA, but this must be considered carefully as patients could be under sedation upon arrival at the hospital. Furthermore, contributing to discrepancies among features relevant for PTE development, the number of participants with bilateral brain lesions in the biperiden group (25/64; 39.0%), was double the number of participants in the placebo group (10/59; 16.9%).

Treatment compliance was assessed based on both the patient's electronic record and the drug accountability provided by the pharmacy and nurse team. In general, patients received mean (SD) 30.95 (11.59) doses of placebo initiating 12.11 (9.99) h after TBI or mean (SD) 25.79 (14.15) doses of biperiden initiating 10.65 (5.84) h after TBI, which is far below the total of 40 planned doses. More specifically, only 31/56 (55.3%) participants received at least 30 of the total of 40 doses (75%) of biperiden. Importantly, it must be considered that patients evolving to death before completing the intervention

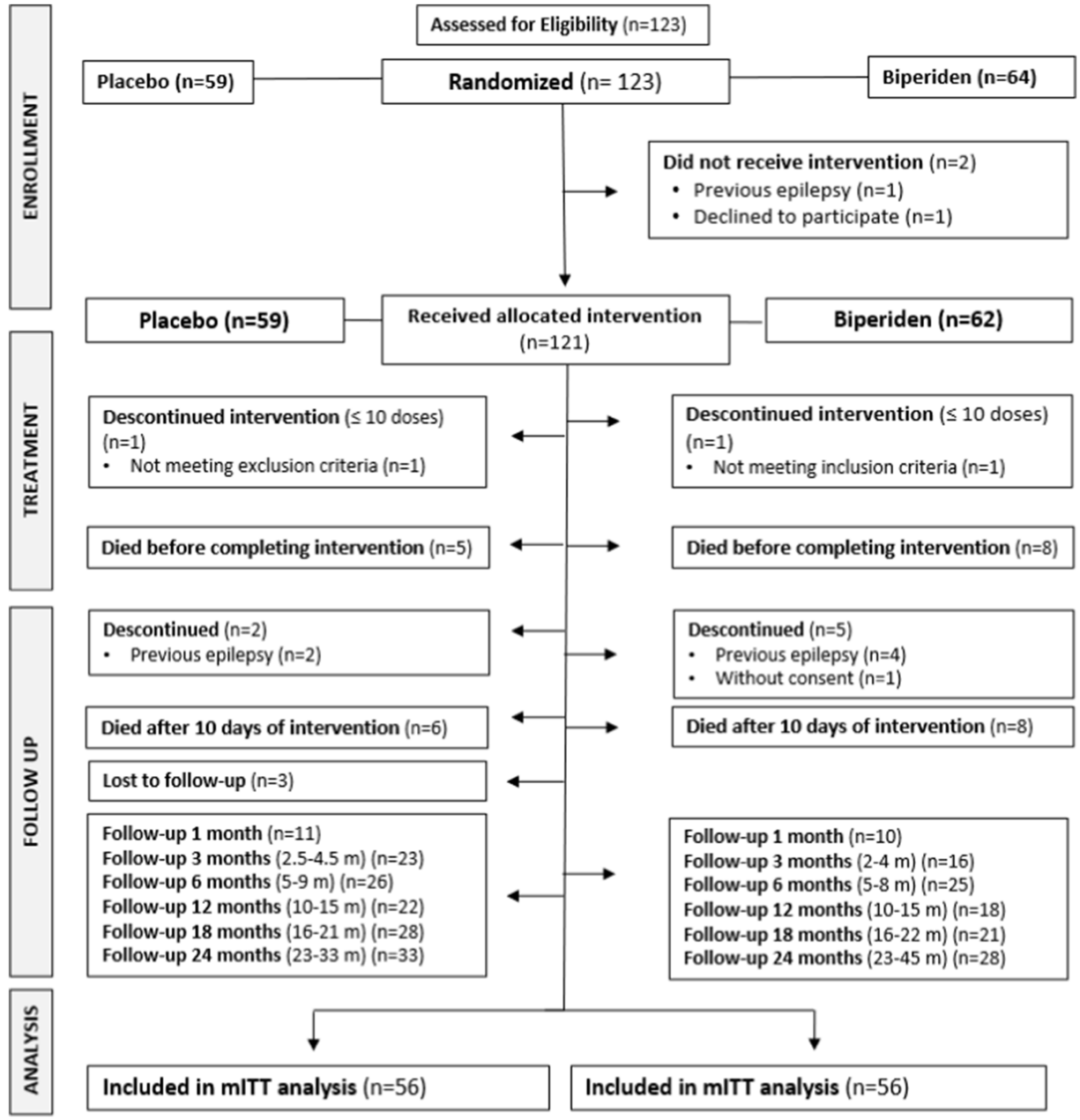


FIGURE 1
Flow diagram of randomized clinical trial for biperiden as antiepileptogenic after traumatic brain injury.

contributed to poor adherence numbers. Even so, biperiden was well tolerated for patients in the context of acute TBI. Constipation (43.9%; placebo $n = 28$, biperiden $n = 26$) and agitation (21.1%; placebo $n = 10$, biperiden $n = 16$) were the most common adverse events observed during the intervention period. Nevertheless, both events were primarily associated with prolonged bed rest and reduced levels of sedation in intensive care patients, respectively for constipation and agitation.

Death cases were mainly attributed to the TBI itself (placebo $n = 9$, biperiden $n = 12$); in other cases, deaths were attributed to injuries in other parts of the body ($n = 1$ placebo), comorbidities ($n = 1$ biperiden), sepsis ($n = 1$ placebo, 583 days; $n = 1$ biperiden, 82 days), malnutrition associated with major depressive disorder ($n = 1$ biperiden, 130 days) and neurologic shock ($n = 1$ biperiden, 214 days). One patient (placebo) had a stroke after 32 months and was not included in the mortality analysis. Cox regression models, both unadjusted and adjusted for GCSoS, showed that there is a lack of evidence regarding group differences for survival (Table 3).

For the primary outcome, 3 placebo patients and 6 patients in the biperiden group developed epilepsy during the two-year follow-up. An additional participant from the biperiden group presented alcohol withdrawal seizures 31 months after TBI, and therefore was not included on PTE analysis. Again, both Cox regression models, unadjusted and adjusted for GCSoS, showed lack of evidence

TABLE 1 Summary statistics of the baseline characteristics of participants by allocated group.

Characteristic	Control (*n* = 59)		Biperiden (*n* = 64)	
	n	mean (SD)	*n*	Mean (SD)
Age, y	59	43.70 (17.68)	64	43.78 (17.66)
GCSoS, score	40	8.75 (4.35)	45	8.51 (4.35)
GCSoA, score	59	7.51 (4.80)	64	7.49 (4.83)
Hospital stay, d	49	29.10 (33.64)	48	28.88 (33.85)

GCSoS, Glasgow Coma Scale on scene; GCSoA, Glasgow Coma Scale on admission.

regarding group differences for this outcome. The same was observed for the competing risk regression. Table 3 also shows the unadjusted and adjusted effects of the intervention for PTE outcome.

For the secondary outcome, the difference in the logs of expected counts of unprovoked seizures is expected to be 2.03 unit higher for biperiden compared to placebo (robust standard error = 0.573, *p*-value <0.001, 95% CI = 0.912 to 3.1597). After the adjustment of GCSoS, the results are close to what was previously reported, the difference in the logs of expected counts of unprovoked seizures, is expected to be 1.857 unit higher for biperiden compared to placebo (robust standard error = 0.762, *p*-value 0.015, 95% CI = 0.263 to 3.351).

Discussion

This first randomized, double-blinded trial of treatment with biperiden versus placebo in patients with acute TBI shows that biperiden is generally safe and well-tolerated when used under the current administration regimen in critical care patients. For the primary outcome, incidence of PTE after TBI, results did not achieve significance when comparing both groups. Similar finding was achieved for survival analysis indicating lack of evidence.

For the secondary measurement, specifically late seizure frequency, this study indicated an increased count of unprovoked epileptic seizures in patients treated with biperiden during the two-year follow-up. In spite of baseline characteristics of groups being statistically similar, patients treated with biperiden tended to show more severe injuries as demonstrated by lower score at GCSoS than patients treated with placebo. Also, bilateral brain lesions were more frequent in the biperiden group. Both characteristics, severe and bilateral lesions, were already described as risk factors for PTE (22). Although statistical differences in seizure frequency were still found among groups even after adjusting for GCSoS in the present study, we speculate that group differences in these parameters might have contributed to difficulties in seizure control, as well as a possible lower ASM adherence following the first PTE seizure, which unfortunately was not controlled in the present study.

Balancing the different experimental groups concerning trauma severity or GCSoS score would have required a distinct experimental design increasing the overall complexity of conducting the trial, which

TABLE 2 Summary statistics of the baseline characteristics of participants by allocated group.

Characteristic		Control (*n* = 59)		Biperiden (*n* = 64)	
		n	%	*n*	%
Female		11	18.6	11	17.1
Age	16–45	33	55.9	38	59.3
	46–88	26	44.0	26	40.6
GCSoS	Mild	17	28.8	10	15.6
	Moderate	3	5.08	5	7.8
	Severe	20	33.8	30	46.8
	Missing	19	32.2	19	29.6
GCSoA	Mild	19	32.2	15	23.4
	Moderate	9	15.2	4	6.25
	Severe	31	52.5	45	70.3
Acute symptomatic seizure (yes)		10	16.9	14	21.8
Neurosurgery (yes)		29	49.1	42	65.6
Phenytoin (yes)		37	62.7	48	75.0
Antibiotics (yes)		39	66.1	49	76.5
Family history of epilepsy	Yes	9	15.2	4	6.25
	No	27	45.7	28	43.7
	Not sure	1	1.69	0	0.0
	Missing	22	37.2	32	50.0
CT evaluation	No lesion	7	11.8	8	12.5
	One lesion	27	45.7	16	25.0
	Two lesions	8	13.5	16	25.0
	Multiple lesions	15	25.4	19	29.6
	Missing**	2	3.38	4	6.25
Lateralization of lesions*	No lesion	7	11.8	8	12.5
	Right hemisphere	21	35.5	14	21.8
	Left hemisphere	19	32.2	13	20.3
	Bilateral	10	16.9	25	39.0
	Missing**	2	3.38	4	6.25
Location of lesions*	No lesion	7	11.8	8	12.5
	Frontal	30	50.8	35	54.6
	Temporal	26	44.0	34	53.1
	Parietal	7	11.8	6	9.37
	Occiptal	3	5.08	2	3.12
	Nucleocapsular region	1	1.69	0	0.0
	Other (insula, cerebellum)	1	1.69	1	1.56
	Missing**	2	3.38	4	6.25
Fracture	Yes	31	52.5	37	57.8
	No	26	44.0	23	35.9
	Missing**	2	3.38	4	6.25

(Continued)

TABLE 2 (Continued)

Characteristic		Control (*n* = 59)		Biperiden (*n* = 64)	
		n	%	*n*	%
Subarachnoid hemorrhage	Yes	29	49.1	35	54.6
	No	28	47.4	25	39.0
	Missing**	2	3.38	4	6.25
Subdural hematoma	Yes	21	35.5	32	50.0
	No	36	61.0	28	43.7
	Missing**	2	3.38	4	6.25
Epidural hematoma	Yes	17	28.8	12	18.7
	No	40	67.7	48	75
	Missing**	2	3.38	4	6.25
Midline shift	Yes	12	20.3	14	21.8
	No	45	76.2	45	70.3
	Missing**	2	3.38	5	7.81
Diffuse cerebral edema	Yes	0	0.0	1	1.56
	No	57	96.6	59	92.1
	Missing**	2	3.38	4	6.25

CT, computerized tomography. *Lesion refers to intraparenchymal hemorrhage and/or contusion. **Missing refers to CT images not found for review.

we could not handle with the available resources. Inclusion criteria in the current study required not only GCS score between 3–12 but in addition TC scan with evidence of contusion or intraparenchymal hemorrhage. Additionally, efforts were made to ensure the treatment initiation time window, grounded on laboratory evidence, to be as soon as possible. Moreover, conducting a double-blind, placebo-controlled intervention in an emergency setting entail achieving a balance that is the least disturbing for the appropriate standard treatment that patients would typically receive, alongside the requisites of the clinical investigation. In conclusion to this aspect, while acknowledging the potential benefits of further defining patient allocation based on lesion aspects, doing so might introduce a significant burden to the study and could considerably compromise its feasibility.

Despite the variability in the incidence of PTE across different studies (23), considering collective findings, an occurrence rate of PTE in the current study would have been anticipated to be around 13–37% (20, 22, 24, 25–29), but the total incidence, 8.03% (9/112), was lower than expected, especially considering the 5.35% (3/56) observed cases for the placebo group. Still, this incidence is higher than the 2.7% diagnosis of PTE described in recent studies (5, 30). Considering this variability, the incidence rate should be carefully rethought to achieve validated sample size calculation through further investigation in the field.

Whereas most studies that present data on the incidence of epilepsy development after TBI typically have an inclusion window of 24 h for intervention, in this study, the interval was restricted to patients admitted in the initial 12 h after injury. There is no reported evidence on any potential influence of the delay for medical assistance after a lesional event and the subsequent development of PTE. Yet it is conceivable that a shorter timeframe for medical intervention might increase the likelihood of a favorable outcome for most medical conditions. In pre-clinical studies, anticholinergic treatment is known to potentially modify the epileptogenic process (10, 31, 32). Specifically, biperiden suppresses spontaneous seizures in animal models of epilepsy. In addition, treatment with biperiden can delay the latency and decrease the incidence and intensity of spontaneous seizures (31). Seconding the hypothesis, a recent paper suggested that scopolamine exerts antiepileptogenic/disease-modifying activity in the lithium-pilocarpine rat model, possibly involving increased remission of epilepsy as a new mechanism of disease-modification (33). Because of the robust results of biperiden and other anticholinergic drugs over suppressing the epileptogenic process in animal models, the inconclusive or even not beneficial use of biperiden in the current trial could be derived from the limitations of this study, as further discussed.

Based on experimental data from animal models it was hypothesized that among the critical factors for an effectiveness for preventing PTE are the time-window for starting treatment after injury, treatment duration and drug dosage. All of those parameters have only been tested in rats and the inferred parameters employed here may need adjustments. Moreover, difficulties were encountered, especially in the beginning of the study, to initiate the intervention within the scheduled 12 h after TCE, since many patients from primary health centers arrived at the tertiary referral hospital at the limit or suppressing this restricted time-window. In addition, ensuring intervention during the first 24 h, especially while patients were unstable or undergoing surgery, as well as maintaining intervention throughout 10 consecutive days, were also challenging, given the diversity of health professionals involved in patient care (whom many times were polytraumatized), and different hospitalization units inside the hospital (which is the largest hospital complex in Latin America). Together these factors contributed to protocol deviations.

Other major issues for this study was related to patient recruitment, which can be explained considering the characteristics of a teaching hospital, with high turnover of neurosurgery medical residents and the complex nature of the trial (unstable patients in the emergency room, need to quickly check eligibility criteria of possible participant, quickly obtain a cranial CT and correctly analyze lesion images, perform the randomization and administration of the first dose within 12 h of trauma), which increased the occurrence of screening failure.

Also as a limitation, while randomization was performed using random numbers generated by statistical software, the allocation of the medication occurred by sequential inclusion of participants, which may have induced potential bias, especially considering that it was not adjusted by trauma severity. Second, operational challenges had to be addressed, mainly related to the low-income characteristic of the population attended by the hospital, which added difficulty to contact and transport participants to follow-up visits, reduced operational research time, and finally the SARS-CoV-2 pandemic involving social distance policies, which limited our ability to adhere strictly to the designed follow-up schedule.

Indeed, the COVID-19 pandemic significantly impacted the study. Initially, patient enrollment was compelled to halt due to the stringent measures imposed as a response to the pandemic. Various countries adopted diverse strategies to manage this severe public health crisis, and there was no clear indication of the duration for which measures like social distancing and remote work would remain in effect. Furthermore, acknowledgement was made of the potential presence of additional variables introduced by the pandemic, which could hinder the amalgamation of data collected

TABLE 3 Results of the Cox regression models.

Outcome	Model	Coefficient	SE	*p*-value	HR	95% CI	
PTE	Unadjusted	0.97	0.70	0.170	2.63	0.65	10,57
	Adjusted	0.99	0.75	0.190	2.70	0.61	11,97
	Adjusted SHR	0.86	0.71	0.229	2.37	0.58	9.61
Survival	Unadjusted	0.45	0.39	0.248	1.57	0.73	3,38
	Adjusted	0.25	0.40	0.529	1.29	0.58	2,85

PTE, post-traumatic epilepsy; SHR, subdistribution hazard ratio derived from the competing risk regression.

before and after the pandemic. Consequently, the determination to conclude the study was made. This decision not only facilitates a more thorough and comprehensive analysis of the results but also paves the way for potential adjustments in preparation for a new clinical trial.

As aforementioned, we did not find clinical evidence for the primary endpoint, the number of patients developing PTE. Unexpectedly, the use of biperiden in patients after TBI might worsen the frequency of seizures in those patients that develop PTE. Supported by these uncertain findings, planning for an experimental design in a new multicenter trial will be refined to incorporate a larger sample size in an efficient time schedule; more restricted inclusion criteria limited only for patients with moderate and severe lesions as per GCS on admission; blind randomization by each center *in loco*, and for each patient (instead of sequentially); electronic case report forms using the RedCap system for data collection, reinforcement of protocol training and of structured research teams. These changes will help to constrain variability and increase study quality.

Despite decades of experimental investigation into the plastic changes that ensue after lesion events in the brain, there has been little progress using this concept into clinical testing. EpiBioS4Rx, a large collaborative effort currently being carried out is expected to yield one or more candidate antiepileptogenic treatments, as well as biomarker information, resources, expertise, and patient populations sufficient to carry out an economically feasible, full-scale clinical trial of at least one antiepileptogenic intervention (16). The results of our study directly anticipate some of the issues that should be considered when designing such trials, including those related with the time window after the precipitating injury.

Conclusion

There was insufficient evidence regarding the effect of biperiden in preventing post-traumatic epilepsy after TBI. The combined effect of variables known to have an impact on the likelihood of developing late post-traumatic seizures and its unbalanced frequency in the different groups is an aspect to be considered and underpins the need for larger studies.

Transparency, rigor, and reproducibility summary

The study design and analysis plan were preregistered on January 13, 2010 at https://www.clinicaltrials.gov/study/NCT01048138, under NCT01048138. Prespecified sample size was 57 per group, yielding statistical power of 80% for detection of an effect size of 5% for the primary outcome measure. All subjects were assigned to biperiden or placebo using a random number generator, yielding groups that did not differ in baseline characteristics. 123 subjects were engaged and primary outcomes were assessed in 112 subjects after 27 deaths and 14 incomplete assessments. All primary outcomes were assessed by investigators blinded to group assignment and could guess the group assignment with accuracy no greater than chance. Biperiden required to perform the interventions are widely available from Cristália (Brazil). Key inclusion criteria were assessed by investigators with professional qualifications (medical residents). Clinical outcomes were assessed by investigators with extensive professional qualifications (neurologists and neurophysiologists). Statistical analysis was performed by researcher with extensive experience in statistical analysis for clinical trials. Ongoing replication studies have been preregistered at https://www.clinicaltrials.gov/study/NCT04945213. De-identified data from this study are not available in a public archive. De-identified data from this study will be made available (as allowable according to institutional IRB standards) by emailing the corresponding author.

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 studies involving humans were approved by Research Ethics Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP; CAAE n 08533513.6.2002.0068) and Universidade Federal de São Paulo (UNIFESP; CAAE n 08533513.6.1001.5505). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

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Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP grant number 2018/24561-5), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil (CAPES; Finance Code 001).

Acknowledgments

The authors thank physicians and nurses from the Neurology Department of HC/FMUSP for assistance with patient's enrollment and data collection, especially Saul Almeida da Silva, Rodrigo Kei Kuromoto, Vitor Yamaki, Renato Vianna, Christiane Cobas, Denise Harumi Nakanishi, Dionasson Altivo Marques, Ramona Oliveira, Jenifer Fleming, Paula Vitoria Correa Ribeiro, Camilla Martins, and Monica A. L. Moraes. We thank Rafael Leite Pacheco and Hugo Cogo Moreira for assistance with statistical analysis. We thank Rachel Riera for critical discussion of the study. We thank Clivandir S. Silva from Unifesp for technical assistance. We also thank Cristália (Brazil) for donating the biperiden used in this study.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 22 August 2024
DOI 10.3389/fneur.2024.1454361

OPEN ACCESS

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RECEIVED 25 June 2024
ACCEPTED 29 July 2024
PUBLISHED 22 August 2024

CITATION
Xue H, Xue K, Wang X, Xu W, Zhang W and Xia G (2024) Chronic subdural hematoma that may be caused by nephrotic syndrome: a case report and literature review.
Front. Neurol. 15:1454361.
doi: 10.3389/fneur.2024.1454361

Chronic subdural hematoma that may be caused by nephrotic syndrome: a case report and literature review

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Background: Chronic subdural hematoma (CSDH) is a common complication of neurosurgery. Craniocerebral trauma is the likely cause. There are no reports relating CSDH with nephrotic syndrome. Its pathogenesis is very rare, and there are no previous reports on treatments for this disease. We report a case of chronic subdural hematoma that may be caused by nephrotic syndrome and review the previous literature on this subject.

Case summary: We report a rare case of chronic subdural hematoma that may be caused by nephrotic syndrome. After the patient was admitted to the hospital, relevant laboratory tests were conducted, and a large amount of protein was detected in the patient's urine, indicating hypoproteinaemia and hyperlipidemia. The patient was diagnosed with nephrotic syndrome. After the exclusion of related surgical contraindications, the patient underwent trepanation and drainage of the chronic subdural hematoma. Subsequent treatment with oral atorvastatin was provided after surgery. The patient was transferred to the nephrology department for further treatment of nephrotic syndrome if his neurological condition improved. No neurological sequelae were detected at the follow-up visit 3 months after the operation.

Conclusion: Chronic subdural hematomas are rarely caused by nephrotic syndrome. Trepanation and drainage may be considered for patients confirmed to have adequate hematoma liquefaction on imaging and who can tolerate craniotomy. Atorvastatin should be supplemented as prophylactic treatment after the operation. Nephrotic syndrome should be treated as soon as the patient's neurological condition is stable.

KEYWORDS

nephrotic syndrome, chronic subdural hematoma, mechanisms, surgery, drugs

Introduction

Chronic subdural hematomas rarely develop as a result of nephrotic syndrome, and there have been no reports worldwide. Surgery is the main treatment method. When hematoma liquefaction is sufficient, trepanation and drainage of chronic subdural hematomas should be performed. When hematoma liquefaction is incomplete or trepanation and drainage fail, craniotomy should be performed to clear the hematoma. Postoperative oral atorvastatin is

necessary. Nephrotic syndrome should be actively treated after the patient's neurological condition is stable.

Case report

A 77-year-old male patient who experienced exacerbated weakness of the bilateral lower limbs for 1 day after experiencing bilateral lower limb weakness for 3 months was admitted to the Neurosurgery Department of Yantaishan Hospital, Yantai City, on January 14, 2024, for treatment. On admission, physical examination revealed that the patient had clear consciousness and was expressive. The bilateral pupils were 3.0 mm in diameter and sensitive to direct and indirect light. The muscle strength of both upper limbs was grade 5, and that of both lower limbs was grade 4. Muscle tension was normal. The bilateral Babinski sign was negative. The patient reported that he was in good physical health in the past. Preoperative brain CT at admission revealed a crescent-shaped low-density shadow in the right frontotemporal parietal area, compression of the lateral ventricle, and a 0.8 cm shift to the left of the midline structure (Figure 1). Magnetic resonance angiography revealed no significant abnormalities. Magnetic resonance angiography show no spinal dural leakage on thoracic and lumbar MR images. No abnormalities were found on CT scan of the lungs. The patient's D-dimer level at admission was 14.19 mg/L, and his 24-h urinary protein concentration was 10903.65 mg. The serum albumin concentration was 23.1 g/L. The total cholesterol level was 6.29 mmol/L, and the LDL level was 4.96 g/L. The classification of nephrogenous albuminuria was as follows: urinary immunoglobulin G > 58.6 mg/L, urinary β_2-microglobulin >4.12 mg/L, urinary microalbumin >348 mg/L, urinary α_1 microglobulin >110 Mg/L, urinary α_2 macroglobulin >18.10 mg/L, and urinary transferrin >15.7 mg/L. Antinuclear antibodies, antiextractable nuclear antigen antibodies, antiphospholipase A2 receptor antibodies, and humoral immunity were not abnormal. Subsequently, trepanation and drainage of chronic subdural hematomas were performed. During the operation, the subdural fluid was viscous and contained more floccules (Figure 2). Figure 3 shows that the humoral cytology results were grade I. A few red blood cells and lymphocytes could be seen in the images, and no dyskaryotic cells could be seen (Figure 3). Routine tests of subdural effusion fluid revealed a white blood cell count of 98000×10^6/L, an 88% composition of multinuclear leukocytes and a positive protein quality (+++). Postoperative CT reexamination revealed that the size of the original subdural hematoma was smaller than that in the preoperative period, the compression of the lateral ventricle was relieved, and the degree of displacement of the midline structure was less than that in the preoperative period (Figure 4). The patient was advised to continue his treatment in the Department of Nephrology after surgery. The patient was followed up by telephone 3 months after surgery, and no residual neurological sequelae were detected.

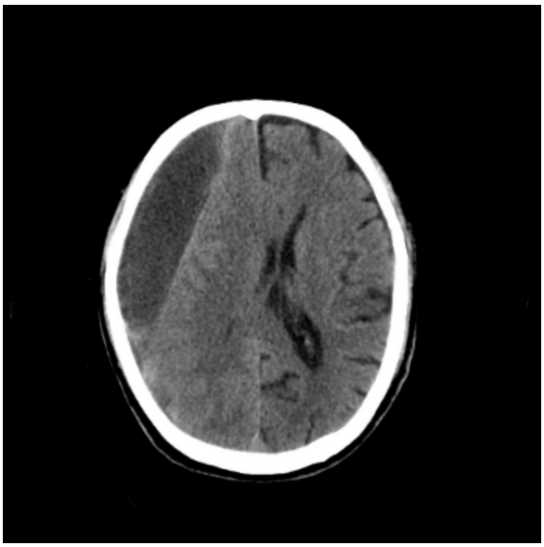

FIGURE 1
Preoperative brain CT revealed a crescent-shaped low-density shadow in the right frontotemporal parietal area, compression of the lateral ventricle, and a 0.8 cm shift to the left of the midline structure.

Discussion

Chronic subdural hematomas are common complications of neurosurgery and are more common in older men. The overall incidence of CSDH ranges from 1.72 to 20.6 per 100,000 persons per year (1). At present, head trauma is believed to be the factor most likely to contribute to the formation of a chronic subdural hematoma (2), but our patient had no history of craniocerebral trauma. Other rare causes include malignant tumors (3), hematological disorders (4), and spinal dural leakage (5). No related malignancies, hematological abnormalities, or spinal dural leakage on thoracic MRI or lumbar MRI were found in our patient before the operation. After the above etiology was excluded, nephrotic syndrome was considered the likely cause of the disease. There have been no reports

FIGURE 2
The subdural effusion fluid was thicker, with a large amount of flocculent materials.

worldwide thus far, and there are only a few reports of cerebral hemorrhage caused by nephrotic syndrome. The likely cause of this disease has yet to be determined.

Hu P noted that hypoalbuminemia directly affects red blood cell deformability and possibly affects endothelial function (6). According to the Cox proportional hazards model conducted by Seliger and colleagues, a 1-g/dL decrease in the serum albumin concentration was associated with a 43% increased risk of stroke among patients with end-stage renal disease (7). Our patient's serum albumin concentration was 21.3 g/L, which indicates hypoproteinaemia. This factor may be involved in the occurrence and development of the disease.

In 2010, Solak et al. suggested that nephrotic syndrome may be secondary to amyloidosis (8), which is a common cause of cerebral hemorrhage. This finding is consistent with the conclusion of the study performed by Niculae (9) in 2017. These authors suggested that small blood vessel damage caused by amyloidosis immune deposition is a common cause of cerebral hemorrhage. Notably, amyloidosis often leads to lobar hemorrhage; however, there are no reports related to chronic subdural hematoma. However, in 2013, Kitamura et al. reported that an acquired factor V inhibitor is a rare bleeding disorder that is known to be difficult for physicians to treat because of their limited knowledge and uncertain relationship with autoimmune disease (10). They suggested that acquired factor V inhibitors can cause both nephrotic syndrome and intracranial hemorrhage (10). However, owing to limited knowledge and its uncertain relationship with autoimmune diseases, additional studies are needed.

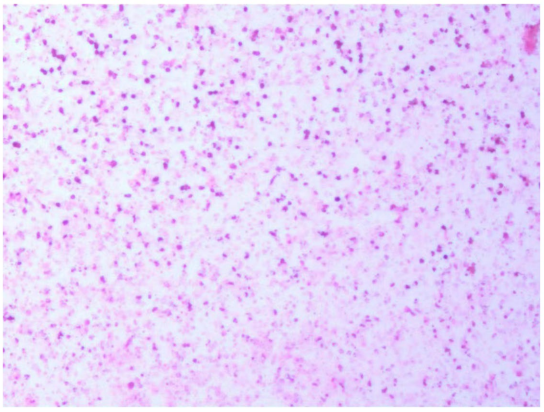

FIGURE 3
Humoral cytology indicating grade I. A few red blood cells and lymphocytes are visible in the picture, and no dyskaryotic cells are visible.

Considering the pathogenesis of our case, the possible mechanism is as follows: (1) Amyloidosis occurs in both the kidney and brain. The medial and outer membranes of intracranial blood vessels are replaced by amyloid protein. Abnormal vascular endothelium increases the permeability of blood vessels; thus, various plasma components, including proteases, can invade the blood vessel wall, resulting in intimal hyalinoid thickening. The blood vessel wall contains fibrinoid necrotic components, which increase the fragility of blood vessels and are prone to rupture and bleeding. (2) Some specific types of nephrotic syndrome are associated with acquired FV inhibition, and these coagulation disorders may be the cause of intracranial hemorrhage. Damage to small blood vessels is aggravated by hypoproteinaemia-induced red blood cell deformability and possible endothelial dysfunction. Notably, the continuous accumulation of blood in the subdural space induces chronic inflammation and the formation of highly permeable new capillaries (11), which may also be involved in the further development of this disease.

There are two main surgical treatment methods for chronic subdural hematoma: trepanation and drainage, as well as craniotomy for hematoma evacuation. Owing to their long-term clinical applications, the safety and effectiveness of trepanation and drainage for chronic subdural hematoma have been widely recognized. These are currently the most widely used methods (12, 13). Craniotomy for hematoma evacuation followed by the placement of a large bone flap is rare because of the high risks of trauma and postoperative complications (14). However, nephrotic syndrome puts the human body in a state of hypercoagulation, so the hematoma is more likely to coagulate and form massive floccules that block the drainage tube,

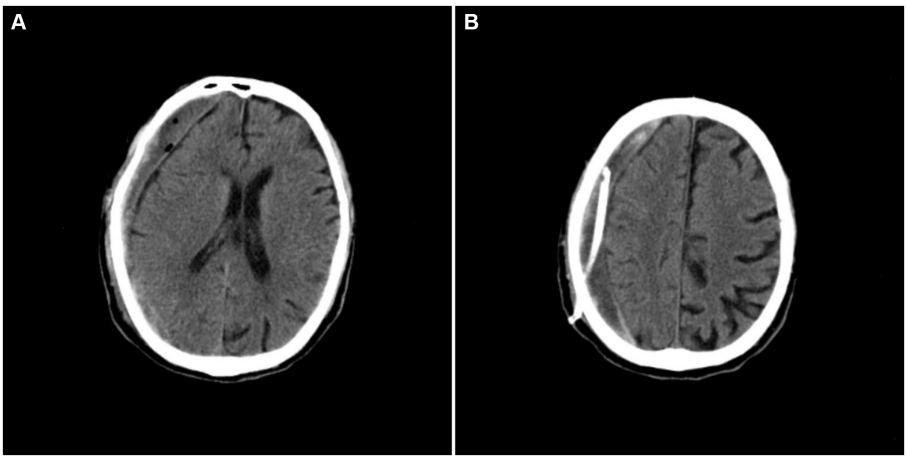

FIGURE 4
Postoperative craniocerebral CT revealing that the subdural hematoma was smaller in size, the compression of the lateral ventricle was relieved, and the degree of displacement of the midline structure was reduced.

which may lead to poor results or even failure of trepanation and drainage. Therefore, the authors suggest that patients who have adequate liquefaction of chronic subdural hematomas and can tolerate craniotomy should undergo trepanation and drainage. If the drainage effect is poor and liquefaction of the hematoma is not obvious, craniotomy is recommended to clear the hematoma if the patient can tolerate it.

In a preliminary study, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase was first reported to reduce the hematoma volume in CSDH patients (15). Atorvastatin inhibits inflammatory angiogenesis and promotes vascular maturation by reducing macrophage infiltration and downregulating vascular endothelial growth factor, monocyte chemotactic-1, tumor necrosis factor-α and transforming growth factor-β_1 (16). And previous research has shown that atorvastatin is an effective conservative therapy of chronic subdural hematoma (17). After surgery, our patient was treated with oral atorvastatin.

Nephrotic syndrome is likely to recur if it is ineffectively treated with surgery. Recurrence is considered related to excessive fluid leakage due to increased capillary permeability caused by hypoproteinaemia. Therefore, the treatment of nephrotic syndrome is crucial.

In summary, chronic subdural hematomas caused by nephrotic syndrome are extremely rare and have no typical clinical manifestations. The following characteristics often indicate the possibility of chronic subdural hematoma caused by nephrotic syndrome: (1) Severe proteinuria and decreased serum albumin concentrations are present. (2) In addition to neurological symptoms, there are clinical manifestations such as edema, susceptibility to infection, oliguria, and anuria. (3) Chronic subdural hematoma without a history of trauma. When the above characteristics appear, the possibility of chronic subdural hematoma caused by nephrotic syndrome should be considered.

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 studies involving humans were approved by the Yantaishan Hospital Affiliated to Binzhou Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

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Funding

The author(s) declare no financial support was received for the research, authorship, and/or publication of this article.

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

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TYPE Review
PUBLISHED 17 September 2024
DOI 10.3389/fneur.2024.1423329

OPEN ACCESS

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RECEIVED 25 April 2024
ACCEPTED 02 September 2024
PUBLISHED 17 September 2024

CITATION
Zhang D, Sheng Y, Wang C, Chen W and Shi X (2024) Global traumatic brain injury intracranial pressure: from monitoring to surgical decision.
Front. Neurol. 15:1423329.
doi: 10.3389/fneur.2024.1423329

Global traumatic brain injury intracranial pressure: from monitoring to surgical decision

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Traumatic brain injury (TBI) is a significant global public health issue, heavily impacting human health, especially in low-and middle-income areas. Despite numerous guidelines and consensus statements, TBI fatality rates remain high. The pathogenesis of severe TBI is closely linked to rising intracranial pressure (ICP). Elevated intracranial pressure can lead to cerebral herniation, resulting in respiratory and circulatory collapse, and ultimately, death. Managing intracranial pressure (ICP) is crucial in neuro-intensive care. Timely diagnosis and precise treatment of elevated ICP are essential. ICP monitoring provides real-time insights into a patient's condition, offering invaluable guidance for comprehensive management. ICP monitoring and standardization can effectively reduce secondary nerve damage, lowering morbidity and mortality rates. Accurately assessing and using true ICP values to manage TBI patients still depends on doctors' clinical experience. This review discusses: (a) Epidemiological disparities of traumatic brain injuries across countries with different income levels worldwide; (b) The significance and function of ICP monitoring; (c) Current status and challenges of ICP monitoring; (d) The impact of decompressive craniectomy on reducing intracranial pressure; and (e) Management of TBI in diverse income countries. We suggest a thorough evaluation of ICP monitoring, head CT findings, and GCS scores before deciding on decompressive craniectomy. Personalized treatment should be emphasized to assess the need for surgical decompression in TBI patients, offering crucial insights for clinical decision-making.

KEYWORDS

traumatic brain injury, intracranial pressure, decompressive craniectomy, TBI management, Glasgow Coma Scale

Introduction

Traumatic brain injury (TBI) is the leading cause of disability and death among young people worldwide. TBI often leads to increased intracranial pressure, reducing cerebral perfusion pressure and causing cerebral ischemia (1). In particular within low-and middle-income countries, the incidence of TBI is the highest, and the mortality rate is also the highest (2). Severe TBI (sTBI) Management depends on mitigating secondary brain injury (3–5). In this scenario, medically refractory intracranial hypertension after sTBI is the most common cause of death (6). Monitoring intracranial pressure (ICP) is essential in managing severe traumatic brain injury, guiding both pharmacological and surgical treatments (7). The National Brain Trauma Foundation guidelines recommend the use of invasive ICP monitoring

(IIB level of evidence) (8). To reduce secondary brain damage, high ICP is associated with high mortality and dysfunction in TBI patients. It is currently believed that patients with severe TBI require immediate treatment when the ICP is >22 mmHg (8). However, there has been controversy about this threshold in clinical management. At present, there is no level I evidence to support the use of clinical interventions to target a specific ICP threshold (9). Decompressive craniectomy (DC) stands as a crucial measure in mitigating intracranial pressure among patients, playing a pivotal role in their management (10, 11). Nevertheless, the efficacy of decompressive craniectomy in the treatment of severe head injury has remained a subject of ongoing controversy (12). Craniectomy decompression has the potential to trigger a range of intricate complications, it can even result in severe sequelae (13). Despite the ongoing controversy surrounding it, craniectomy decompression remains the ultimate life-saving procedure for patients suffering from refractory intracranial hypertension. For patients with refractory intracranial hypertension, there is no clear consensus on whether doctors continue to perform conservative treatments for decompression or immediately perform decompressive craniectomy (14). Regarding patients with refractory intracranial hypertension, there exists a lack of a clear consensus among medical professionals on whether to persist with conservative treatment methods for decompression or promptly proceed with decompressive craniectomy (15). The aim of our narrative review is to concisely elaborate on the significance and worth of contemporary intracranial pressure monitoring in patients presenting with elevated intracranial pressure, while simultaneously delving into the prevailing challenges and dilemmas surrounding its application. The main focus of the final review is to summarize the thorough assessment of ICP monitoring, head CT findings, and GCS scores for clinical surgical decisions.

In this review, we conducted a comprehensive evaluation of the disparities in morbidity and mortality rates associated with TBI across various income countries. Furthermore, we delved into the advancements made in ICP monitoring among TBI patients and discussed the application of ICP monitoring across different income nations. At the same time, the role of decompressive craniectomy in patients with TBI is summarized. Finally, we put forward ideas for the direction of future research and clinical services.

The epidemiology of TBI

The majority of the global population resides in low-and middle-income countries (LMIC), where the prevalence of TBI is very high. TBI poses a significant public health challenge, imposing a substantial economic burden on both nations and the world at large (16). The incidence of TBI in LMIC is triple that of high-income countries (HIC), as indicated by available data (17). Utilizing mathematical modeling, researchers have estimated the incidence of TBI in nations with varying income levels globally. The incidence of TBI in low-and middle-income countries accounts for 72% of the global incidence of TBI, and the results are listed in Figure 1A (17). In these countries, acquiring adequate healthcare resources remains a significant challenge. People living in low-and middle-income nations face a much higher risk of fatality from severe TBI, with the likelihood being twice as high as that in high-income countries (18). The total number of deaths is shown in Figure 1B. The decrease in mortality rates among patients with severe TBI in high-income countries may potentially stem from disparities in the quality and accessibility of medical care. TBI patients frequently exhibit a concomitant elevation in ICP. According to estimates, the ICP monitoring rate in the United States is 77.4% (19), Australia and New Zealand is 44.5% (20), Canada is 63% (21), and Europe is 37% (22), 11% in China (23), the data is shown in Figure 1C. In high-income countries, the rate of brain injuries among the elderly is gradually climbing, with a growing proportion of these injuries being caused by falls (24). In low-and middle-income countries, road traffic collisions continue to top the list as the leading cause of brain trauma (25). These epidemiological data consistently demonstrate significant disparities in the occurrence of TBI between high-income countries and their low-and middle-income counterparts. For low-and middle-income countries, individualized treatment may be required based on the clinical experience of clinicians. In comparison to HICs, the scarcity of intensive care capabilities among neurosurgeons in LMICs poses a significant hindrance to effective management, given that LMICs often have limited access to intensive care, and even in capable situations. The available resources are also very limited (26). Consequently, in numerous low-and middle-income countries, patients suffering from severe TBI are unable to receive proactive and comprehensive intensive care. Nursing interventions such as body position and tracheal suctioning can affect the change of intracranial pressure in patients with TBI (27, 28). Nursing operations should be carried out under close monitoring (2). In developed nations replete with a plethora of medical resources, TBI might exhibit relatively consistent trends, irrespective of external factors such as nursing interventions. However, In LMICs, limited medical resources often lead to insufficient numbers and capacity of medical personnel to meet patient needs (29). The implementation of intracranial pressure management methods recommended by guidelines, such as deep analgesia, sedation, and muscle relaxation, is frequently difficult to implement (8). Because analgesia and sedation necessitate continuous vigilant bedside monitoring by nurses, muscle relaxation demands a titrated treatment. The vast majority of patients failed to undergo therapeutic interventions deep sedation for the purpose of reducing intracranial pressure, nor were they administered muscle relaxation titration therapy (30). This led to significant variability in the ICP levels observed among TBI patients. Therefore, TBI management guidelines based on intracranial pressure are difficult to be properly applied in low-and middle-income countries. A multicenter randomized controlled trial (RCT) conducted in the integrated ICU of LMIC (such as Bolivia and Ecuador) compared the differences between two TBI management strategies, one of which was based on ICP and the other did not (31). In view of the increasing differences in resources and epidemiology between LMIC and HIC, the trials conducted in this case may not be enough to show that management based on ICP monitoring has no advantages (32). In the future, conducting more RCT studies for low-TBI populations in low-and middle-income countries is a key direction.

However, a preponderance of studies and clinical trials pertaining to TBI are typically conducted in high-income nations, and some patients recruited to LMIC should be given more attention (19). Translating HIC research findings to LMICs is challenging due to their limited access to intensive care and scarce resources, even when available. A recent survey revealed that LMIC neurosurgeons' lack of

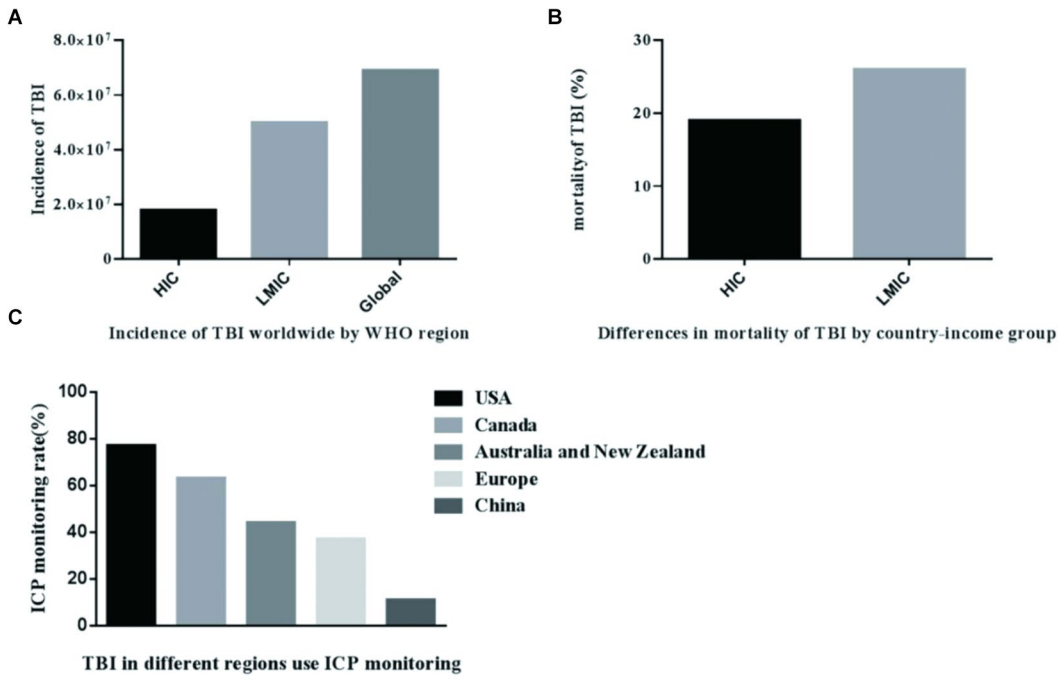

FIGURE 1
Incidence rate of TBI in countries with different income levels in the world. **(A)** Incidence of TBI worldwide WHO region. **(B)** Differences in mortality of TBI by country-income group. **(C)** TBI in different regions use ICP monitoring.

intensive care competence, in contrast to HICs, poses a significant hurdle in patient management (33).

The importance and role of intracranial pressure monitoring

Neurosurgery patients with TBI are critically patients, and their condition changes rapidly (34). ICP is one of the main complications of traumatic brain injury (33). A substantial body of cohort studies has consistently demonstrated that ICP is independently associated with an elevated risk of mortality and poor prognosis. Therefore, the core of strict management of TBI patients lies in the management of elevated ICP (35–37). According to the changes in ICP, combined with the changes in the patient's consciousness, pupils and vital signs, it can be timely and accurately judged and found changes and the development of the patient's condition and timing of effective rescue (38). ICP monitoring can accurately reflect changes in intracranial pressure (39). According to the Fourth Edition Guidelines of the Trauma Foundation (8), TBI patients presenting with a GCS score ranging from 3 to 8 and exhibiting abnormal head CT scans should undergo ICP monitoring upon regaining consciousness. Abnormal CT scans of the head typically encompass a range of pathologies, including hematoma, contusion, swelling, herniation, and compression of the basal cistern (40). Furthermore, for patients who have sustained severe TBI and been admitted to the hospital with normal cranial CT scans, intracranial pressure ought to be meticulously monitored if they exhibit ≥2 of the following characteristics: age over 40 years; unilateral or bilateral limb dyskinesia; systolic blood pressure (blood pressure) < 90 mmHg (41). The consensus among experts, as outlined in these guidelines, underscores the necessity for ICP monitoring and management of patients suffering from TBI. In an observational study, the implementation of ICP monitoring correlated with a diminished risk of fatality (42). A study utilizing a vast prospectively collected database analyzed the impact of ICP reduction interventions on the 2-week mortality of patients with severe TBI treated with or without an ICP monitor. In patients with severe TBI who are treated with intracranial hypertension, the use of an ICP monitoring can significantly reduce the mortality rate compared with patients who are not treated with an ICP monitoring (43). Another study delved into the trials and case series pertaining to the treatment of severe closed TBI, meticulously analyzing both the mortality rates and the favorable outcomes 6 months post-injury. Active ICP monitoring and treatment of patients with severe TBI can significantly improve the prognosis (44). A prospective observational study meticulously assessed the impact of intraventricular ICP monitoring on the prognosis of elderly patients suffering from severe TBI. It has been found through research that the implementation of intraventricular ICP monitoring can mitigate the gravity of in-hospital mortality rates among geriatric patients who have sustained TBI, and improve their 6-month post-injury prognoses (45). A Meta-Analysis since the third edition of "Brain Injury Treatment Guidelines" shows the results (Including "Indications for Intracranial Pressure Monitoring"), with severe TBI monitored by ICP, an excellent survival rate has been observed (46). In cases of severe TBI, an elevation in ICP is intricately linked to mortality and an unfavorable clinical prognosis (47). The main goal of ICP monitoring in TBI is to be able to detect secondary injuries early and implement therapeutic interventions immediately (48). Although a randomized study showed that continuous monitoring of ICP in patients with TBI did not improve the prognosis compared with nursing care, however, based on imaging and clinical examination (49), there are significant

differences in treatment plans between the two groups in this study. It does not endeavor to evaluate the inherent worth of ICP monitoring, but rather employs two distinct methodologies to ascertain the effectiveness of intracranial hypertension management. The core value of ICP monitoring is to guide the correct treatment strategy, so there is no need to use the evidence in this study to show that ICP monitoring has no value or can be used as an argument against the use of ICP monitoring (12). The implementation of long-term continuous ICP monitoring is advantageous, as the patterns of ICP variation can serve as a guiding principle for individualized treatment (50). In addition, ICP monitoring combined with other nervous system monitoring helps to understand the pathophysiological process of injury (51). Drawing upon clinical practice and literature reports, we provide a overview of the specific performance of ICP monitoring. The value of the following aspects: (a) Early judgment of the patient's prognosis; (b) Judge whether to perform craniotomy and decompression, and determine the surgical strategy; (c) Early diagnosis of delayed intracranial hematoma, as an early warning; (d) Guide clinical treatment, such as the application of dehydration drugs, the time course of mild hypothermia treatment; and (e) Determine the surgical effect of bone flap surgery. A series of typical clinical studies are shown in Table 1, which shows the application value of ICP monitoring in traumatic brain injury.

The current state of ICP monitoring technology and the future direction

The conventional ICP monitoring technique involves the direct implantation of a pressure sensor within the brain, subsequently connecting the pressure monitoring device to the exterior. This approach boasts the benefits of straightforward operation and precise pressure measurement (52). In contemporary medical practice, two prominent technologies, namely External Ventricular Drains (EVD) and Intraparenchymal Fiberoptic Monitors (IPM), stand as the preferred and recommended technology for intracranial pressure monitoring (53). At the same time, EVD can also drain cerebrospinal fluid to achieve the therapeutic purpose of reducing intracranial pressure (54). EVD is considered the gold standard. The conventional techniques employed for the monitoring of ICP are invasive in nature,

TABLE 1 Clinical trial of useful value of ICP monitoring in patients with traumatic brain injury.

	Sample	Number of patients	Study design	Outcomes
Chiara Robba et al. (2021) (85)	Patients aged 18 years or older who were admitted to the ICU with either acute brain injury due to primary haemorrhagic stroke or traumatic brain injury	2,395	Prospective observational cohort study	6 month mortality was lower in patients who had ICP monitoring (441/1318 [34%]) than in those who were not monitored (517/1049 [49%]; $p < 0{\cdot}0001$).
Lele A et al. (2019) (86)	Patients over 18 year with severe TBI (admission Glasgow coma scale score < 8) who received tracheal intubation for at-least 48 h were examined	200	a secondary analysis of a prospective cohort study	ICP monitor placement without cerebrospinal fluid drainage within 72 h of admission was associated with reduced in-patient mortality.
Qiang Yuan et al. (2016) (87)	Patients with severe diffuse TBI (GCS score on admission <9 and Marshall Class II-IV)	482	Retrospective cohort	ICP monitor placement was associated with a significant decrease in 6-month mortality after adjustment for the baseline risk profile and the monitoring propensity of patients with diffuse severe TBI, especially those with GCS scores of 3 to 5 or of Marshall computed tomography classification IV.
Qiang Yuan et al. (2015) (88)	Moderate or severe traumatic brain injury patients who were more than 14 years old	1,443	Retrospective observational multicenter study.	ICP monitoring was significantly associated with an improved 6-month mortality for patients with TBI who had a GCS score of 3–5 at admission, had a GCS score of 9–12 at admission that dropped to 3–8 within 24 h after injury
Arash Farahvar et al. (2012) (43)	Patients with severe TBI (GCS Score < 9) treated for intracranial hypertension	1,446	Prospectively cohort	In patients with severe TBI treated for intracranial hypertension, the use of an ICP monitor is associated with significantly lower mortality when compared with patients treated without an ICP monitor
Bennett TD et al. (2012) (89)	Children (age < 18 years) with TBI and head/neck Abbreviated Injury Scale (AIS) score ≥ 3 who were ventilated for ≥96 consecutive hours or died in the first 4 days after admission	4,667	Retrospective cohort study	Hospitals that monitor ICP more often and hospitals with higher patient volumes had better patient outcomes
Walter Mauritz et al. (2008) (90)	Patients with severe TBI (GCS < 9)	1856	Prospective multicenter cohort study	The lowest mortality rates (raw and risk-adjusted) were found in the subgroup with the highest rate (91.1%) of ICP monitoring
Lane PL et al. (2000) (91)	Registered cases of TBI	9,001	Study of case records	The insertion of an ICP monitor is associated with a statistically significant decrease in death rate among patients with severe TBI

which can potentially result in a series of complication. These include, but are not limited to, intracranial infections, intracranial hematomas, and damage to brain tissues (55–58). In addition, the utilization rate of ICP monitoring technology in low-and middle-income nations remains exceptionally low. This may be attributed to the technical intricacies of ICP monitoring, as well as its prohibitively high cost (59). The optimal ICP monitoring device should exhibit precision, dependability, and cost-effectiveness, while concurrently imposing minimal morbidity (60). Therefore, the establishment of a non-invasive and simple bedside ICP monitoring method is of great value for trauma first aid. Prior research has revealed a positive correlation between changes in the optic nerve sheath diameter (ONSD) and ICP (61). However, it is worth noting that measurements of ONSD may encounter interference from the presence of papilledema (62). The Erasmus Medical Center in the Netherlands conducted clinical trials aimed at dynamically tracking alterations in ICP and analyzing whether such changes directly influence the measured value of ONSD. They discovered that the utilization of ultrasound measurement for ONSD in individuals suffering from TBI serves as a swift, straightforward, and efficacious approach (63). Accurate ICP non-invasive monitoring method, with ONSD≥5.0 mm as the critical value, accurately judge the increase of ICP (>20 mmHg) (64). This technology can be used in injured sites, emergency rooms and other places where invasive ICP monitoring cannot be implemented. In addition, compared with other literature reports using CT to measure the diameter of the optic nerve sheath, the ultrasonic measurement method can reflect ICP more simply and in real time, and is practical for clinical use (65). An observational study confirmed that the combination of ONSD and estimated ICP (eICP) using transcranial Doppler may improve the accuracy of estimating the occurrence of intracranial hypertension (66).

In fact, non-invasive ICP monitoring encompasses a diverse array of categories, which are outlined as follows: (1) imaging magnetic resonance, tomography, ONSD and other technologies; (2) indirect transmission of ICP, such as TCD and eyeball and ophthalmic artery methods; (3) monitoring metabolic changes, Such as near-infrared spectroscopy; and (4) the registration of functional activities, such as EEG, visual evoked potentials and auditory potentials (67). Theoretically speaking, the concept of a non-invasive technique for measuring intracranial pressure holds significant appeal, primarily due to its reduced tedious action and can avoid circumvent complications like hemorrhage and infection (68). The utmost priority thing is that the price is not too high. In the future, we aspire to conduct randomized clinical trials to substantiate the clinical impact of utilizing non-invasive techniques for intracranial pressure measurement.

How to manage the elevated intracranial pressure

The role of decompressive craniectomy in patients with TBI

Decompressive craniectomy (DC) is a neurosurgical intervention in which a part of the skull is removed to mitigate the pathological escalation of ICP, avert the occurrence of cerebral herniation, and prevent the onset of cerebral tissue ischemia (69). This surgery procedure holds the potential to improve cerebral hemodynamics and oxygenation in patients suffering from elevated ICP (70, 71). Furthermore, in certain instances, it can contribute to the reduction of mortality rates and disabilities among those afflicted with TBI (56). In patients with worsening cerebral edema, it effectively provides extra space for the swollen brain and reduces the risk of further elevation of ICP and brain herniation (57). The basic principle of DC is to remove a part of the skull, transforming the originally closed cranial cavity into a relatively open state, thereby changing the fixed capacity and limited ICP of the cranial cavity (72). Ever since the early 2000s, there has been a concerted effort not only to improve the pre-hospital care for TBI patients but also introduce well-designed programs and implement ICP monitoring. These advancements have collectively transformed the therapeutic environment of DC. The basic principle of decompression surgery is based on the Monro-Kellie law (59). According to this theory, the intracranial volume should be kept constant, and the volume should be compensated by the transfer of cerebrospinal fluid, cerebral blood volume or brain herniation. Removing a variable amount of bone, whether it involves enhancing the openness of the dura mater or augmenting the number through duraplasty, serves as a rapid and efficient approach to expand intracranial volume, thereby effectively reducing intracranial pressure and enhancing intracranial space (73). In recent years, the significant difference in the use of DCs globally has been the practice gap between low - and middle-income countries and high-income countries, which constitutes an important background for clinical decision-making (74). The application of DC surgery in high-income countries is supported by high-quality randomized controlled trials (RCTs) evidence. For example, the study on Neurosurgery at the University of Manitoba in Canada (75) integrated multiple clinical trial results, providing updated guidelines for the application of DCs in sTBI. These studies indicate that timely DC surgery can significantly reduce mortality in patients with refractory intracranial hypertension. High income countries rely on advanced medical technology and comprehensive postoperative management to ensure the safety and effectiveness of DC surgery (76). In contrast, low-income countries face many challenges in the application of DC surgery due to limited medical resources. These countries often lack advanced intracranial pressure monitoring equipment and appropriate nursing techniques, which limits the application of DC surgery (77). However, in emergency situations such as acute traumatic brain injury, DC surgery is still considered an important means of saving lives (78). However, inadequate postoperative management and rehabilitation support may affect the long-term prognosis of patients. Therefore, when formulating a global strategy for DC surgery, it is necessary to fully consider the economic, medical, and social conditions of different countries.

TBI management: optimal strategy for ICP monitoring

Determining the optimal timing for DC necessitates clinicians to possess a more comprehensive understanding of the ICP situation. This requires a complete ICP management plan. Given the significant individual differences among patients suffering from craniocerebral trauma, relying solely on a singular ICP indicator is evidently inadequate as a means to accurately assess prognosis.

Comprehensively, the value of ICP monitoring lies in real-time reflection of dynamic changes in intracranial pressure, providing key

information for clinical diagnosis and treatment decision-making, and improving patient prognosis (79). A recent study has revealed that the score derived from head CT scans and the volume of brain contusion exhibit a correlation with the elevation of ICP (80). Consequently, these influencing characteristics can be harnessed to anticipate the risk of increased ICP in patients with sTBI and corresponding treatment (66). The combination of clinical and head CT examination results that can be used to make management decisions may be an effective strategy, which is also one of the directions of future clinical research. The Glasgow Coma Scale (GCS) provides a convenient method for quickly assessing the level of consciousness of TBI patients (67), but the GCS score alone cannot provide enough information to guide surgical decision-making. Therefore, elucidating the surgical requisites of patients should be combined with this information. Hence, we stress the importance of a comprehensive evaluation of ICP monitoring, head CT findings, and GCS scores for surgical decision-making to ensure a more reliable approach, particularly in specific scenarios. However, in high-income countries, despite the relatively abundant technological resources, the limited availability of technological resources and the significant differences in decision-making between high-tech medical services still exist (81). ICP monitoring, as the "gold standard" that directly reflects changes in intracranial pressure, is limited in its widespread application in all cases due to its high cost and operational complexity (82). In contrast, CT scanning has become the preferred method for preliminary assessment of traumatic brain injury due to its wide availability and relatively low cost (83). However, CT scanning has limitations in dynamically monitoring changes in intracranial pressure, and continuous observation of GCS scores has become an important supplementary tool to help doctors assess patients' consciousness status and degree of neurological damage (84). Therefore, in the decision-making process, it is necessary to comprehensively consider the patient's specific condition, treatment goals, resource cost-effectiveness, and potential risks in order to make the optimal treatment choice.

Conclusion and future directions

ICP monitoring combined with clinical manifestations and head CT imaging results can comprehensively evaluate the patient's condition. We emphasize the importance of comprehensive evaluation of ICP monitoring, head CT results, and GCS scores for decision-making on whether to perform surgery, providing guidance to clinical doctors based on specific indications to ensure personalized and optimized treatment.

Author contributions

DZ: Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. YS: Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. CW: Writing – original draft, Visualization, Software, Resources, Investigation, Data curation, Conceptualization. WC: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. XS: Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. Special Fund for Economic and Technological Development in Longgang District, Shenzhen (Grant no. LGKCYLWS2021000005).

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

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frontiers | Frontiers in Behavioral Neuroscience

TYPE Review
PUBLISHED 08 October 2024
DOI 10.3389/fnbeh.2024.1326115

OPEN ACCESS

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RECEIVED 22 October 2023
ACCEPTED 20 September 2024
PUBLISHED 08 October 2024

CITATION
Chan A, Ouyang J, Nguyen K, Jones A, Basso S and Karasik R (2024) Traumatic brain injuries: a neuropsychological review. *Front. Behav. Neurosci.* 18:1326115. doi: 10.3389/fnbeh.2024.1326115

Traumatic brain injuries: a neuropsychological review

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The best predictor of functional outcome in victims of traumatic brain injury (TBI) is a neuropsychological evaluation. An exponential growth of research into TBI has focused on diagnosis and treatment. Extant literature lacks a comprehensive neuropsychological review that is simultaneously scholarly and practical. In response, our group included, and went beyond a general overview of TBI's, which commonly include definition, types, severity, and pathophysiology. We incorporate reasons behind the use of particular neuroimaging techniques, as well as the most recent findings on common neuropsychological assessments conducted in TBI cases, and their relationship to outcome. In addition, we include tables outlining estimated recovery trajectories of different age groups, their risk factors and we encompass phenomenological studies, further covering the range of existing—promising tools for cognitive rehabilitation/remediation purposes. Finally, we highlight gaps in current research and directions that would be beneficial to pursue.

KEYWORDS

traumatic brain injury (TBI), neuropsychology, review, assessment, head injury, trauma, neuroscience, psychology

Introduction

It is possible to speculate that the non-linear path of evolution and its violent history, may have led to the development of brains that favored protection and recovery from brain injuries. To name a few, human brains are protected by the cranium, underneath which are three core layers of protective membranes, in addition to being immersed in cerebrospinal fluid capable of absorbing impact. Indeed, recovery has been found through neuroplasticity and neurogenesis, which appear to be far more advanced than previously believed. At some point however, there was a trade-off, the advancement of brain structure and function, for a brain more susceptible to damage through impact. This adaptation functioned because it was predicated on the utility of complex cognitive abilities to offset and/or treat the consequences of Traumatic Brain Injuries (TBI). One way this is expressed in modern day is the development of neuropsychological assessments in service of evaluating, predicting, and improving the outcome of a TBI.

While TBIs were likely around since the dawn of humankind, it is also likely that our brains did not evolve to withstand the impact of a car crash. Nonetheless, when viewing incidence rates, it is clear that comparable injuries our ancestors might have sustained (e.g., from falls, sports, or violence) continues to be a major problem. Worldwide, traumatic brain injuries (TBI) constitute one of the leading causes of injury-related deaths and disability (Maas et al., 2022).

TBIs are responsible for ∼30% of all injury-related deaths in the United States and are a leading cause of mortality and disability (Kaur and Sharma, 2018). Closed-head injuries (CHI) account for about 75% of TBIs, while penetrating head injuries (PHI) account for around 25% (CDC, 2016). There were ∼223,125 TBI-related hospitalizations in 2019 and 64,362 TBI-related deaths in 2020 (CDC, 2022). TBI is the leading cause of death and disability in people younger than age 35 in the US (Popescu et al., 2015). Falls lead to nearly half of the TBI-related hospitalizations and are now the leading cause of TBI, overtaking road traffic accidents (Roozenbeek et al., 2013). Firearm-related suicide is the most common cause of TBI related deaths in the US. In the United States, around 1.7 million people suffer TBI, with older adolescents (ages 15–19 years) and older adults (ages 65 years and older) among the most likely to sustain a TBI (Georges and Das, 2023).

Traumatic Brain Injury (TBI) refers to penetrating, blunt, or acceleration/deceleration force-derived craniocerebral injury. TBI often results in cognitive deficits in memory, attention, processing speed, word finding, planning, and problem-solving. From a behavioral perspective, difficulties such as lack of initiative, irritability, and poor temper control may be present. Somatic symptoms may include headaches, dizziness, fatigue, sleep disturbance, poor balance, and coordination. TBI can also result in psychological symptoms (e.g., anxiety and depression). These difficulties usually resolve to some degree, but could persist in many cases, even decades after injury. Thus, ongoing assessment and tailored interventions are crucial for effectively managing TBI. Neuropsychological assessments are essential for identifying deficits and understanding the extent of functional loss. These assessments predict outcomes and guide treatment, aiming to improve patients' functional abilities while mitigating further cognitive decline. The specific characteristics of a TBI, including the nature and extent of the damage, help determine the type of neuropsychological deficits that may arise. Understanding these characteristics will assist in distinguishing between different forms of head injuries and their impacts.

Types of traumatic brain injuries

Head injuries can be classified into two broad categories: closed head injury (CHI) and penetrating head injury (PHI) (Kaur and Sharma, 2018). CHI is more common and complicated than PHI; over 75% of all brain injuries are CHIs. CHI occurs when an external force impacts the skull, causing damage to the brain without penetrating the skull. Swift forward or backward movement and shaking of the brain inside the cranium are common causes of this type of damage, which results in hemorrhage and the tearing of brain tissue and blood vessels (Vieira et al., 2016). CHIs can affect various areas of the skull, including the frontal bone, temporal bone, parietal bone, and occipital bone, depending on the specific circumstances of the injury (Jeyaraj, 2019). Paradoxically, while the cranium is meant to protect the brain, in certain circumstances, parts of it may cause damage. One such area is the crista galli, a protruding triangular surface rising from the ethmoid bone that plays a role in attaching the dura mater (one of the protective membranes mentioned earlier).

On the other hand, PHI occurs when a foreign object, such as a bullet or a sharp projectile, penetrates the skull and directly damages the brain tissue. It is important to note that PHI can cause significant damage to the brain tissue, as the object can cause both primary and secondary injuries to the brain. Primary and secondary injuries are two distinct phases of TBI that can cause damage to the brain tissue (Ng and Lee, 2019). Primary injury occurs immediately after the traumatic event, caused by the direct physical forces applied to the brain tissue. Secondary injury occurs after the primary injury and can be caused by various processes, including inflammation, oxidative stress, excitotoxicity, and others. These processes may worsen the symptoms of the initial injury and inflict more harm on the brain tissue. Secondary injuries can occur over a period of hours or days after the initial trauma and can contribute significantly to the long-term effects of TBI.

CHI can range in severity from mild concussions to severe TBI. In mild cases, the individual may experience symptoms such as headaches, dizziness, and confusion but may not lose consciousness. Severe CHI can result in long-term neurological deficits and disability. Symptoms of closed head injuries can include loss of consciousness, memory loss, difficulty concentrating, seizures, and changes in personality or behavior.

In contrast, PHI is typically more severe and life-threatening than CHI. The severity of a PHI depends on the location and extent of the damage caused by the foreign object. In general, PHIs result in more localized brain damage, whereas CHIs may result in diffuse damage to the brain. PHIs may thus yield a neurocognitive profile with more targeted deficits. This may however, be complicated by hemorrhaging, infection, and swelling, further damaging the brain tissue. Treatment for penetrating head injuries often involves surgical removal of the foreign object, followed by intensive medical care to manage the resulting brain damage and complications. Recognizing the distinction between closed and penetrating head injuries provides context regarding the diverse nature of TBI and their specific effects on brain regions, with these varying impacts directly influencing cognitive and functional outcomes.

Multiple levels of analysis

The short and long-term sequelae of PHIs and CHIs depend on severity and may be analyzed on multiple levels. Linear and rotational acceleration of the brain can result in mild TBI (mTBI) if a significant amount of force is applied. Blennow et al. (2016) have shown that in these instances, the lower sulci located in the frontal, parietal, and temporal lobes receive higher levels of stress and strain induced by TBI. Cortices and white matter tracts also receive the brunt of the damage induced by mTBI. White matter tracts, which send neuronal signals to nearby neurons and are located in subcortical regions, corpus callosum, fornices, and cerebellum, are more prone to damage upon the initial impact of mTBI.

One of the most common symptoms caused by TBI is cerebral edema. This symptom occurs after the injury and is triggered by an inflammatory response (Arulsamy et al., 2018). Cortical swelling is typically increased in the prefrontal and temporal cortices (Linden et al., 2019; Dall'Acqua et al., 2017). Prolonged and sufficient damage from TBI has the potential to induce an inflammatory response (Bigler, 2013; Johnson et al., 2013) with acute swelling

potentially leading to chronic secondary injuries (Ma et al., 2016). That is why, when swelling is severe enough, a portion of the skull may be removed (i.e., craniectomy) to enable the inflammatory processes to take their course, and naturally subside without risking further damage to the brain. Compared with controls, once swelling has subsided, many individuals diagnosed with TBI exhibit reduced brain volume in the temporal, hippocampal, and frontal regions (Bigler, 2013).

Upon impact, axonal shearing may occur near the primary site of injury (Govindarajan et al., 2016). Occurring in areas of the brain initially injured, axonal shearing has been identified as a precursor to the buildup of beta-amyloid plaques, apoptosis, and oxidative stress (Ma et al., 2016). Damage to these areas plays a large role in the symptoms that are experienced. TBI has been shown to produce emotional deficits, challenges with working memory, and other executive dysfunctions. The hippocampus has been correlated to memory related processes and aids in the regulation of emotions. Damage to this area caused by TBI can result in decreased memory capacity and emotional functioning. However, studies have shown that promoting neurogenesis within this region can reduce negative symptoms (Peng and Bonaguidi, 2018).

Moderate to severe TBI significantly reduces cortical thickness (Vedung et al., 2022). Differences in cortical thickness in acute and chronic stages of TBI demonstrate how an injury in the frontal-temporal region correlates to neurodegeneration across the hemispheres. For example, a study was conducted comparing the cortical thickness of mTBI patients where a baseline of decreased cortical thickness was established compared to healthy controls (Govindarajan et al., 2016). Research conducted by Govindarajan et al. (2016) demonstrated that cortical thinning is associated with mTBI primarily in the frontal, temporal, and parietal regions. Follow up examinations of cortical thickness in these subjects revealed the thinning had spread to include some areas of the insula and cingulate cortex (Govindarajan et al., 2016). Research has shown that cortical thickness decreases in adolescents who tested positive for TBI in the prefrontal cortex (Linden et al., 2019). Vedung et al. (2022) established a correlation between a decrease in cortical thickness and an increase in TBI symptom severity, in particular, individuals with moderate to severe TBI exhibit increases in cortical thinning compared with control groups. Within their study, Govindarajan et al. (2016) provided treatment for an mTBI subgroup, participants did not show a significant reduction in cortical thickness after obtaining treatment.

Mild TBI also commonly decreases. However, in some instances, sporadic increases in cortical thickness have been shown to occur post-mTBI, but the increase is not significant compared to cortical thinning (Govindarajan et al., 2016). Individuals who have worse outcomes long term, over 3 months, after the initial injury have lower volumes of gray and white matter and increased cortical thickness compared with healthy controls (Dall'Acqua et al., 2017). The subsequent increase of cortical thickness in mTBI patients has not been well-established, but it could indicate an increase in swelling and trauma.

White and gray matter are largely affected by TBI (Vedung et al., 2022; Dall'Acqua et al., 2017). A decrease in white and gray matter volume inhibits homeostasis as these regions are responsible for neuronal communication and processing. The continuous degeneration of white and gray matter is also found in the neuropathology of neurodegenerative diseases suggesting that secondary injuries of TBI correlate to those diseases (Jang et al., 2017). Jang et al. (2017) found a relationship between the degeneration of white and gray matter tracts and Alzheimer's, Subcortical Vascular Dementia, and mixed dementia, with the highest level of white matter degeneration occurring in Subcortical Vascular Dementia and mixed dementia. The varied impact of TBI on specific brain areas results in diverse experiences and outcomes, with differences observed in cortical thickness, white and gray volume, and the manifestation of secondary injuries.

Findings on how TBIs may impact cortical thickness, white and gray matter, major lobes of the brain, the hemispheres and particular regions may orient the clinician toward specific functions that may be anticipated to be impacted. Yet, real-time dysfunction may be more accurately depicted by a network approach, analyzing neurodynamic imbalances between networks within the brain. Recognizing how TBI disrupts these interconnected networks informs the injury's impact on both localized brain functions and broader cognitive processes.

Neural networks and TBIs

While there are many neural networks, there are three of particular interest, the Default Mode Network (DMN), the Salience Network (SN) and the Central Executive Network (CEN). The DMN is a network related to mind wandering, autobiographical recall, prospection, self referential processing, and social cognition. The SN determines the significance or salience of external or internal stimuli in any particular moment. It also acts as a toggle between the DMN and CEN. The CEN is a network dedicated to goal-directed tasks and executive functioning. Mutual inhibition typifies the relationship between the DMN and CEN (Chan, 2021). These three networks are typically working together in neurodynamic balance, as the individual shifts their focus toward the external world to focus on a task (CEN) or pauses to reflect on themselves and an interaction that occurred (DMN). In TBIs, intra-network and inter-network disruptions result in broad imbalances and cognitive dysfunction.

From the intra-network perspective, Zhou et al. (2012) have shown that mTBI leads to altered connectivity within the Default Mode Network (DMN), marked by reduced connectivity in posterior regions like the posterior cingulate cortex (PCC) and increased connectivity in the medial prefrontal cortex (mPFC). This imbalance between anterior and posterior regions of the DMN was closely linked to deficits in executive function and mental flexibility, suggesting that such network disruptions may be at the root of some cognitive difficulties commonly observed in mTBI patients. The hyperconnectivity within the mPFC demonstrated an inverse relationship with mood related symptoms such as depression and anxiety. It was further interpreted that the mPFC may initially compensate to sustain cognitive abilities; however, over time, this could contribute to the emergence of psychological symptoms like anxiety and depression.

From an inter-network perspective, Liu et al. (2024) note that it is typical for there to be increased dysconnectivity

between the DMN and CEN in mTBI, which has been correlated to reduced working memory performance; abnormal coupling between the CEN and SN which has related to increased emotional dysregulation and internetwork irregularities between the SN and DMN, which has led to disinhibition. Their novel insights come from analyzing the neurodynamic imbalances from a temporal perspective. In comparison to healthy controls, the mTBI group spent the most time in a state characterized by reduced connectivity between the DMN and SN (state 1), whose length of time correlated to reduced scores on the Montreal Cognitive Assessment. Significantly less time was found in a state characterized by higher DMN connectivity, and negative correlation between the DMN and SN (state 3) whom the authors hypothesized may relate to reduced social cognitive abilities. Finally, mTBI participants also demonstrated overall reductions in the amount of transitions between networks.

Disruptions in other networks such as the SN and CEN have also been observed in mTBI. Liu et al. (2020) documented that mTBI patients frequently exhibit hyper-connectivity between the DMN and SN, potentially acting as a compensatory strategy to preserve cognitive performance in the wake of injury. However, this hyper-connectivity may eventually become maladaptive, contributing to further network imbalances and cognitive decline over time. The impact of these network disruptions is not confined to isolated cognitive functions. Research by Li et al. (2020), Li F. et al. (2023), Li X. et al. (2023), and Li C. et al. (2023) demonstrates that mTBI can disrupt connectivity across multiple networks, including the DMN, SN, CEN, and SMN. These disruptions are strongly associated with impairments in attention, executive function, and memory, highlighting the role of network integrity in the cognitive recovery process following injury. Specifically, decreased connectivity between the SN and executive control regions, such as the superior frontal gyrus, relate to the challenges mTBI patients face in maintaining cognitive performance.

In parallel, Rigon et al. (2016) found that mTBI leads to significant reductions in inter-hemispheric functional connectivity (FC) within externally oriented networks (EONs) such as the fronto-parietal network (FPN) and executive control network (ECN), rather than within the DMN or sensorimotor network (SMN). These specific disruptions in inter hemispheric connectivity were associated with impairments in visuospatial and organizational skills, as evidenced by poorer performance on the Rey-Osterrieth Complex Figure Test (ROCFT), implicating inter-hemispheric FC within executive control and flexibility (Rigon et al., 2016).

Structural damage, such as diffuse axonal injury (DAI), significantly impairs key neural networks like the DMN, SN, and CEN. DAI, which occurs in about half of all severe head trauma cases, involves extensive white matter damage that is correlated with cognitive deficits (Aquino et al., 2014). The severity of DAI correlates with its location: mild cases typically involve the frontal and temporal lobar white matter, moderate cases affect the corpus callosum, and severe cases extend to the dorsolateral midbrain. This damage to white matter tracts, particularly in regions like the corpus callosum and midbrain, is a primary contributor to the network disruptions observed in mTBI, leading to cognitive impairments (Aquino et al., 2014).

While the previous studies focused on spatial dynamics between and within networks of the brain, Alhourani et al. (2016) explored temporal dynamics, focusing on frequency-specific changes in connectivity following mTBI. Their study found that mTBI reduces alpha band connectivity and generates slow delta waves, both associated with white matter deafferentation and subsequent cognitive impairments. These frequency-specific disruptions, particularly within the DMN, are linked to deficits in higher cognitive functions such as memory and attention, which are commonly reported post-concussion (Alhourani et al., 2016). Additionally, the observed network topology changes, including the loss of inter-hemispheric connections, may be related to DAI's impact on white matter tracts like the corpus callosum, further exacerbating cognitive deficits in mTBI patients (Alhourani et al., 2016).

Neuropsychological functions and TBIs

In the context of such foundations as what TBIs are, how they are classified, and how the brain is typically impacted from multiple perspectives, specific neuropsychological functions may now be reviewed in depth. Damage to specific areas (i.e., frontal-temporal cortices and hippocampus) produce the deficits associated with sustaining TBI. As the previously mentioned areas are most vulnerable, the following impaired functions discussed are hallmarks of TBI.

Wang et al. (2021) found support through their research that information processing, memory, and attention are impaired. Individuals with TBI show hyperactivation in the prefrontal cortex, which can lead to cognitive fatigue compared with healthy controls (Gillis and Hampstead, 2015). A review by Blennow et al. (2016) found that impairment of the prefrontal cortex presents difficulty concentrating and poor memory. Additional symptoms related to all severity levels of TBI include nausea, dizziness, vomiting, sensitivity to light, and headaches. Mood changes can also be seen in TBI patients such as an increase in irritability. The treatment of cortical and structural areas resulting in improved functioning that had been damaged by TBI reinforces the role the brain regions play in a healthy brain and what processes are disrupted upon injury.

The prefrontal cortex connects to the limbic system and facilitates top-down processing; damage of these connections correlates to deficits in emotional processing (van der Horn et al., 2015). Emotional impairments are common symptoms of TBI and deficits in processing positively correlate with impairments in accurately identifying negative emotions in individuals with TBI (Rosenberg et al., 2015). Individuals may experience decreased emotional responses or inability to control stronger emotions such as anger (Rassovsky et al., 2015). Axonal shearing of white matter tracts is related to a decrease in general processing speed (Boccia et al., 2022; Ferraracci et al., 2021). This disruption may correlate to damage to the prefrontal cortex. Individuals with TBI compared with healthy controls have demonstrated slower processing speeds (Dymowski et al., 2015). In addition, slowed processing speed, induced by TBI, can affect working memory (Gorman et al., 2016).

TABLE 1 TBI severity, classifications, and characteristics.

	Mild TBI	Moderate TBI	Severe TBI	
Loss of consciousness (LOC)	<30 min (if present)	30 min−24 h	>24 h	Rauchman et al., 2022
Glasgow Coma Scale (GCS)	13–15	9–12	3–8	Williams et al., 2022
Post-traumatic amnesia (PTA)	<24 h	24 h–<7 days	>7 days	French et al., 2015
Prevalence of cases	75–80%	10–15%	<10%	Laccarino et al., 2018; Mckee and Daneshvar, 2015

TBI may also lead to affective disorders, with anxiety, depression, and PTSD being the most common. Anxiety symptoms, irritability, fatigue, and cognitive deficits persist well-beyond 3 months after the initial impact of TBI (Lamontagne et al., 2022; McMahon et al., 2014). Deficits in language and verbal memory occur consistently with TBI (Wang et al., 2021; Ryan et al., 2015b). The duration of these deficits may depend on the age of the individual when they sustained a TBI and the severity classification. Adults aged 18–24 with TBI had language processing return to normal functioning by 6 months post-injury (Coffey et al., 2021). However, other studies suggest that patients/individuals aged 5–15 years may suffer from language deficits for up to 2 years after the initial impact of TBI (Ryan et al., 2015b). The severity of TBI correlates to the severity of symptoms experienced. Age and severity are variables affecting the degree of potential recovery from damage caused to the brain. Continued research in this area could be useful in determining rehabilitation techniques to reduce the duration of deficits after TBI.

Classifying the severity of TBIs

The severity of a TBI is a significant factor that affects both the outcomes and therapies for patients (Rauchman et al., 2022). The degree of severity may increase the risk for cognitive deficits, motor impairment, and emotional difficulties (depression, anxiety, aggression, impulse control, etc.), both temporarily and permanently (Mckee and Daneshvar, 2015). Understanding the similarities and differences between these severity levels is crucial for accurate diagnosis, prognosis, and potential treatment methods. Table 1 is a table which his typically used to help classify the severity of a brain injury. Neuropsychologists are responsible for determining the length of Post-Traumatic Amnesia (PTA), a state of discontinuous cognitive functioning, classically characterized by anterograde and retrograde amnesia. One common task administered is the Galveston Orientation and Amnesia Test (GOAT), whereby the TBI patient must receive a score of 75 or greater on three consecutive trials on independent days to be determined out of PTA.

Imaging tools play a crucial role in determining the severity of TBI and guiding appropriate treatment strategies. These tools provide valuable insights into the structural and functional changes that occur in the brain following an injury (Mckee and Daneshvar, 2015). By visualizing the affected areas and their extent, imaging techniques enable healthcare professionals to accurately assess the severity of TBI, identify potential complications, and monitor the progression of the condition over time. The following table (Table 2) provides a summary of commonly used techniques and their advantages.

Severity of TBIs and neuropsychological profile

The complexity of TBI-related impairments encompasses cognitive deficits, functional limitations, and behavioral changes. Cognitive deficits, including attention, memory, and executive function impairments, pose challenges in cognitive processes. Functional limitations affect individuals' ability to perform daily activities independently, while behavioral changes can have implications for emotional wellbeing and social interactions (Devi et al., 2020). Behavioral problems following TBI present a significant challenge, yet interventions targeting these problems have received limited attention compared with cognitive and functional deficits (Yeates et al., 2017). Treatment approaches primarily focus on addressing the cognitive and functional aspects of TBI, which can have a profound impact on an individual's daily functioning, work performance, and overall quality of life. Various injury-related factors, such as TBI severity, complications, pre-existing injuries to other body regions, and the duration of the injury, influence the manifestation of TBI symptoms (Rabinowitz and Levin, 2014).

Traumatic brain injury ranges from mild, moderate to severe. Mild TBI (mTBI) is more commonly referred to as concussions. Symptoms experienced in mTBI typically do not exceed 3 months, but they tend to subside within 7–10 days. In cases of mild TBI, individuals may experience temporary cognitive impairments, including difficulties with attention, memory, and information processing speed. Additionally, they may encounter mild functional limitations, such as changes in coordination, balance, and fine motor skills. Fortunately, these deficits are usually transient and tend to resolve relatively quickly. Understanding the neurobiological underpinnings of cognitive impairments and emotional changes following TBI provides valuable insights into the mechanisms involved. Research suggests that mTBI can lead to alterations in synaptic function and plasticity. Disruptions in synaptic strength, which refers to the ability of neurons to communicate effectively, can impair neural communication and impact cognitive processes and overall brain function (Witowski et al., 2019). Rapid changes in synaptic strength may be a contributing factor to attention deficits, memory problems, and learning difficulties commonly observed following mTBI.

In moderate TBI cases, cognitive impairments tend to be more pronounced and long lasting, involving attention and memory difficulties, executive function deficits, and reduced information processing speed. Functional impairments in moderate cases may include persistent motor coordination difficulties, challenges in performing activities of daily living, and emotional and behavioral changes. Severe TBI often leads to severe and persistent cognitive impairments affecting multiple domains, such as attention,

TABLE 2 TBI imaging tools.

	Description	When to use	Interpretation	Strengths	
Computed tomography (CT)	Utilizes X-rays to produce cross sectional images of the brain.	Acute phase of TBI to identify bleeding or swelling.	Identifies bleeding, swelling, fractures, or other acute injuries in the brain.	Quick, readily available, effective at detecting fractures and acute bleeding.	Lolli et al., 2016; Power et al., 2016; Schweitzer et al., 2019
Magnetic resonance imaging (MRI)	Uses powerful magnetic fields and radio waves to create detailed images of the brain.	Assessing brain structure, detecting subtle changes.	Detects structural abnormalities, contusions, hemorrhages, or diffuse axonal injury in the brain.	Provides excellent anatomical detail, can reveal contusions, hemorrhages, and diffuse axonal injury.	Lee et al., 2021
Diffusion tensor imaging (DTI)	Variant of MRI that focuses on mapping white matter tracts and assessing their integrity.	Assessing white matter connectivity and abnormalities.	Indicates disruptions in white matter tracts and connectivity, providing insights into the extent of brain damage.	Visualizes neural connections, detects white matter damage, helpful in understanding the impact on brain pathways.	Douglas et al., 2015; Mckee and Daneshvar, 2015
Functional MRI (fMRI)	Measures blood flow and oxygenation changes to assess brain activity and connectivity.	Evaluating functional consequences of TBI.	Shows alterations in brain activity, connectivity, and functional consequences of TBI.	Provides insights into brain function, detects activity changes, reveals connectivity disruptions.	Mckee and Daneshvar, 2015; Scheibel, 2017
Positron emission tomography (PET)	Involves injecting a radioactive tracer to measure brain metabolism and blood flow.	Evaluating brain metabolism and activity.	Highlights areas of altered metabolism, decreased activity, or abnormal glucose utilization in the brain.	Reveals metabolic changes, identifies areas of reduced activity or abnormal glucose utilization.	Huang et al., 2022
Single-Photon Emission Computed Tomography (SPECT)	Involves injecting a radioactive tracer to measure brain blood flow and activity.	Assessing cerebral blood flow and brain activity.	Indicates regions with reduced blood flow, abnormal activity, or functional impairments in the brain.	Helps identify regions of decreased perfusion, abnormalities in brain activity, and functional impairments.	Gosset et al., 2022

memory, language, problem-solving, and executive functions. Furthermore, functional impairments in severe cases can manifest as severe physical disabilities, significant limitations in self-care tasks, difficulties with speech and swallowing, and cognitive and behavioral impairments (Mckee and Daneshvar, 2015). TBI also disrupts the balance of neurotransmitters in the brain, leading to alterations in mood regulation and cognitive functioning (Ahmed et al., 2017). Severe TBI can disrupt emotional contagion, making it difficult for individuals to empathize with others' feelings and maintain social relationships (Rushby et al., 2013). This means they may struggle to pick up on non-verbal cues, misunderstand emotional expressions, and react inappropriately in social situations. This impairment is linked to damage in key brain regions responsible for emotional contagion, like the amygdala and prefrontal cortex (Rushby et al., 2013).

When assessing TBI, different approaches can be taken. As previously discussed, imaging tools are a proficient manner in which to examine this condition and see physical damage to the brain. Another approach to gauging the severity of TBI is to specifically look for difficulties with attention, memory, processing speed, working memory, coordination, and executive functioning. Pen and paper, and computer tests that are administered by a trained professional can acquire such information. These tests inform the clinician to what degree the patient may be experiencing cognitive impairments. Deficits in cognitive functioning are seen in acute and chronic phases of TBI (Tsai et al., 2021).

As research accumulates, so does the opportunity exist for the synthesis of literature that may enable a convenient path for more precise neuropsychological testing. As an example, previous meta-analytic work demonstrates that particular neuropsychological functions were strongly correlated with functional outcome. Allanson et al. (2017) found that delayed verbal memory, visuo-spatial construction, set shifting, and generativity particularly stood out as significant predictors of functional outcome. A more recent meta-analysis supports and builds upon these findings (Krynicki et al., 2023), some of which is presented in Table 3.

TBI impairs various cognitive functions including memory and executive functions. Alongside these cognitive deficits, TBI has been associated with altered affect and subjective emotional states. Forceful trauma may disrupt neural substrates and subsequently neurotransmitters altering emotions (Ahmed et al., 2017). Often, emotional disruptions experienced following TBI are displayed as behaviors and emotional reactions that cannot be accurately classified by the Diagnostic and Statistical Manual for Mental Disorders (DSM-V) (Shields et al., 2015). Decreased executive functioning coupled with the disruption of neurotransmitters as a result of TBI can have profound effects on emotional regulation. Large correlations are shown between emotional regulation and executive functioning self and informant report forms in an acquired brain injury sample of 64% were a result of TBI (Stubberud et al., 2020). Screening for emotional deficits after TBI improves the care clinicians provide. Emotional measures adequate for assessing mood disruptions in TBI populations is provided in Table 4.

Recovery in children, adolescents, adults, and elderly

The trajectory of healing after traumatic brain injury (TBI) is significantly influenced by an individual's developmental stage.

TABLE 3 TBI cognitive function diagnostic tools.

Test	Research findings	Demographic	References
Test of premorbid functioning (TOPF)	The TOPF has a moderate correlation with Full Scale Intelligence Quotient (FSIQ) ($r = 0.77$). TOPF/demographic is a significant predictor of post-injury FSIQ and displays moderate correlation in predicting FSIQ ($R^2 = 0.617$, $p < 0.001$). TOPF predicted 35% of variance in FSIQ. Premorbid intelligence of note, TOPF underestimated 31% of premorbid functioning and only accurately identified 38%. VCI in the WAIS-IV predicted greater variance (55%), and may be better alternative individuals with TBI who previously had a high average to superior intelligence.	Participants were accepted into the study if they suffered TBI including mild, moderate, and severe ($n = 155$).	Joseph et al., 2019
Test of memory and malingering (TOMM)	TOMM was best in detecting feigning in TBI (sensitivity = 98.4%) when compared to Groningen Effort Test, the b test and DCT.	Systemic Review and meta-analysis. 82/664 identified studies used.	Azeredo et al., 2024
Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) or (WISC—for children)	Controlling for effort and malingering, the WAIS IV detects different levels in performance comparing mild/moderate TBI to severe TBI and healthy controls. The severe TBI group performed significantly poorer than the mild/moderate group in processing speed (PSI) ($p = 0.001$) and FSIQ ($p = 0.026$). Severe TBI had significant reductions on all indices (excluding Matrix Reasoning). Mild/moderate TBI compared to controls had significant reductions in Working Memory Index (AR, LN), Processing Speed Index (SS, CD), and perceptual reasoning subtest (BD). Looking specifically at PSI, adequate sensitivity was shown at 89% and poor specificity at 40%.	Clinical populations diagnosed with either mTBI, moderate TBI or severe TBI ($n = 100$).	Carlozzi et al., 2015
Brief Visual Memory Test- Revised (BVMT-R)	Overall classification accuracy: 59%. Perceptual reasoning significantly influenced BVMT-R performance. It is thus important to use the BVMT-R in tandem with other instruments. The test appeared more sensitive to moderate-to-severe TBI than complicated mild TBI.	Clinical participants: 18–75 years, n =100, diagnosed with TBI, no significant premorbid neurological illness, developmental disorders, or psychiatric conditions requiring hospitalization	Donders et al., 2022
Rey-Osterrieth Complex Figure (Rey-O)	Performance validity tests (PVTs) embedded in the Rey-O provide adequate levels of sensitivity and specificity and excellent classification for area under the curve (AUC). Results show that there is excellent classification accuracy using the Sugarman logistic regression formula model 1 and 2 (AUC = 0.80, AUC = 0.83) and Lu and colleagues' equation (AUC = 0.84). A cutoff score of ≥0.45 for Sugarman Model 2 provides 54.1% sensitivity and 97.9% specificity. A cutoff score of ≥0.35 for Sugarman Model 1 provides 43.2% sensitivity and 97.9% specificity. A cutoff score of ≤50 for Lu equation provides 48.6% sensitivity and 95.7% specificity. The Rey-O has sufficient embedded performance validity tests for TBI populations.	Clinical veteran population that meets criteria for mTBI ($n = 100$).	Ashendorf, 2019
California Verbal Learning Test, Second Edition (CVLT-II)	The moderate-severe TBI group performed significantly worse on recall and recognition ($p < 0.0006$ and $p < 0.0008$) compared to controls. The mTBI group performed significantly worse than the control group ($p < 0.02$). Sensitivity for recall discriminability is 74.42 and 60.47% for recognition discriminability.	Clinical population ($n = 43$) moderate-severe TBI ($n = 57$ mTBI), and non-clinical population ($n = 100$).	Jacobs and Donders, 2007
Wechsler's Memory Scale	Significant differences were found between groups on the five index scores ($p < 0.0001$) and 10 subtests ($p < 0.0001$). Regarding TBI severity level and the 10 subtests, a moderate effect size was found for mild-moderate TBI and large for severe TBI compared to the normative sample.	Clinical population ($n = 100$) diagnosed with mild/moderate TBI (35%) and severe TBI (65%). Included a health control group for further comparison.	Carlozzi et al., 2013
Color-Word Interference Test (CWIT-4), Delis Kaplans Executive Function System (DKEFS) Color Word Stroop Test	The color inhibition/switching tasks detect differences between moderate/severe TBI and mTBI. Moderate/severe TBI group performed significantly worse than mTBI ($p < 0.03$). The results show the switching and inhibition/switching subtests can distinguish between moderate/severe TBI groups and mild uncomplicated TBI/control groups (sensitivity = 0.64, specificity = 0.67). Moderate-severe TBI group show what is considered a significant decrease in selective attention ($p = 0.008$) compared to controls, also known as an increase in the magnitude of selective interference. The moderate-severe TBI also show a significant increase in dimensional imbalance ($p = 0.028$) compared to controls. Results indicate TBI affects speed of processing. Sensory processing is also affected with TBI participants having an increased latency naming color on color neutral words compared to reading color neutral words ($p = 0.96$, $p < 0.001$).	Clinical TBI sample ($n = 128$) and health controls ($n = 56$). Moderate-severe TBI group ($n = 324$) and healthy control group ($n = 501$).	Anderson et al., 2017; Ben-David et al., 2011
Connors' Continuous Performance Test, Third Edition (CPT-III)	Controlling for effort and malingering, TBI severity significantly correlates to four CPT-II domains. They were greatest for commissions ($r = 0.463$, $p < 0.001$) and detectability ($r = 0.414$, $p < 0.001$); with the others being omissions, and variability.	Clinical population diagnosed with mTBI ($n = 30$), moderate TBI ($n = 12$), and severe TBI ($n = 18$) compared to healthy controls ($n = 30$).	Zane et al., 2016

(Continued)

TABLE 3 (Continued)

Test	Research findings	Demographic	References
Trail Making Test, A and B (TMT)	The TMT-B ($r = 0.29$; 95% CI 0.17–0.41) had a significant moderate relationship to functional outcomes. The TMT-B was also associated with a person's ability to return to driving ($r = 0.3890$; 95% CI 0.2678–0.5103). Participants were administered the WAIS-IV and other neuropsychological tests. Regression analysis show that motor, processing speed, backwards span, and sustain components are significant predictors of Trails A ($R^2 = 0.45$, $p < 0.02$). Trails B is significantly predicted by forward span, processing speed, and backward span ($R^2 = 0.33$, $p < 0.02$). TMT-C reflects deficits commonly found in TBI. The TMT-C is adjusted from the TMT with 15 circles per page that contain letters and numbers, not 25 circles. This is for both parts A and B.	Meta-analysis of 24/720 studies Children and adolescents previously diagnosed with TBI ($n = 61$). Sample includes mild, moderate, and severe cases of TBI.	Krynicki et al., 2023; Thaler et al., 2013
Verbal fluency (FAS/animals)	Effect size increased with severity. Verbal fluency task are strong indicators of executive dysfunction and language abilities. Effect sizes were moderate to large, phonemic fluency (rs = 0.48) and semantic fluency (rs = 0.45)	Systematic review and meta-analysis of TBI in children: 123/1,516 studies. Meta-analytic review in adults: 1,269 participants, 30 studies	Cermak et al., 2021; Henry and Crawford, 2004
Wisconsin Card Sorting Test– 128 Computer Version (WCST-128)	Compared to healthy controls, TBI patients> perseverative errors, and severe TBI > moderate or mild TBI. Participants with TBI were administered the WCST to examine the relationship between test performance and functional outcomes. Results show that the failure to maintain set errors significant predicts occupational outcomes in TBI patients ≥ 1 year post injury ($\beta = 0.40$, $p < 0.05$). The WCST ($r = 0.20$; 95% CI 0.02–0.37) was significantly associated with functional outcomes.	Review of 47/312 studies Clinical population diagnosed with severe TBI ($n = 143$) Meta-analysis of 24/720 studies	Gómez-de-Regil, 2020; Beng et al., 2007; Krynicki et al., 2023
Clock Drawing	The Extended Glasgow Outcome Scale (GOS-E) used to assess outcomes in TBI patients, shows. significant negative correlations per each domain of the Clock Drawing Test. The clock face ($r = -0.552$, $p < 0.001$), numbers ($r = -0.426$, $p < 0.001$), and hands ($r = -0.511$, $p < 0.001$). Better performance on the Clock Drawing Tests is correlated to decreased scores on GOS-E with better functional outcomes.	Participants who sustained mTBI ($n = 102$), moderate TBI ($n = 30$), and severe TBI ($n = 30$).	de Guise et al., 2011
Grooved Pegboard	Neuropsychological tests were used to determine their level of predictability of real-world driving behavior. The Grooved Pegboard, with an established mean cut-off of 97.5 s, can significantly predict performance of on the road driving in TBI subjects. Sensitivity is 0.82 and specificity is 0.29.	Subjects were diagnosed with TBI or stroke ($n = 78$).	Aslaksen et al., 2013
Balance Error Scoring System	High content validity for concussed or fatigued. Large effect sizes after concussions (1.00–1.32) and fatigue (0.54–1.86). average errors for concussion: 17, and fatigue, 15.8. It may not be valid when differences are more subtle. Overall, the BESS: moderate- good reliability to assess static balance.	Systematic review, 29 articles.	Bell et al., 2011
Halstead-Reitan Battery	The Halstead-Reitan Battery (HRB) assessed TBI severity non-impact, impact and no mTBI groups. Results show the tactile test on the HRB producing significant results between groups ($p = 0.02$). Within the tactile tests, the Tactile Form Recognition Test produced the only significant results ($p = 0.02$) (Sweeney and Johnson, 2017). An additional research conducted by Loring and Larrabee (2006) revealed seven subtests to have large effect sizes between TBI and non-TBI groups. The largest effect size was found in the Impairment Index ($d = 1.77$) (Loring and Larrabee, 2006).	Clinical population of non-impact TBI ($n = 60$), impact TBI ($n = 60$), and healthy controls non-TBI ($n = 29$) (Sweeney and Johnson, 2017). Brain damaged clinical group ($n = 35$) including a closed head injury subgroup ($n = 6$) and penetrating head subgroup ($n = 6$) (Loring and Larrabee, 2006).	Sweeney and Johnson, 2017; Loring and Larrabee, 2006

These stages—childhood (ages < 10), adolescence (ages 10–17), adulthood (ages 18–64), and late adulthood (ages 65+)—mark distinct phases characterized by differing resilience levels and recovery challenges post-TBI. Tailoring interventions to suit these stages optimizes rehabilitation by addressing specific developmental needs and challenges, ensuring more effective functional outcomes and enhanced quality of life.

Many studies suggest that TBI sustained in early childhood tends to have more profound and persistent effects on neuropsychological, psychosocial, and educational outcomes compared with TBI experienced in later childhood (Treble-Barna et al., 2017; Sariaslan et al., 2016; Wade et al., 2016). Younger age and greater TBI severity are linked to poorer functional outcomes (Treble-Barna et al., 2017; Sariaslan et al., 2016; Wade et al., 2016). Age of injury is a critical factor as young children have an increased vulnerability to diffuse brain injury and the harmful effects that such injury may have on their growth and development (Treble-Barna et al., 2017). It is suggested that skills that are rapidly developing during the phase of injury are more susceptible to compromise. Consequently, childhood TBI may pose an increased risk of enduring impairments. TBI severity is another critical factor in functional outcomes, as greater severity is linked to lifelong impairments (Treble-Barna et al., 2017; Sariaslan et al., 2016; Wade et al., 2016). Children with moderate to severe TBI tend to display

TABLE 4 TBI emotional function diagnostic tools.

Test	Research findings	Demographic	References
Beck Depression Inventory-II	BDI-II was broken into four subcategories (somatic symptoms, loss of self-worth, affective symptoms and apathy symptoms) with the intent to distinguish apathy from depression. The apathy subscale and a daily activity log filled out by the participants had a significant negative correlation ($p = 0.009$ and $r = -0.29$). As apathy scores from the BDI-II increased, reported frequency of daily activity decreased. Self-worth and apathy also correlated to a separate measurement of apathy ($p = 0.002$ and $r = 0.32$; $p < 0.001$ and $r = 0.52$).	Participants had a TBI or brain lesion and were recruited from an outpatient clinic in Kyoto, Japan.	Ubukata et al., 2021
Beck Anxiety Inventory (BAI)	The BAI was given to an mTBI veteran population alongside the Neurobehavioral Symptom Inventory (NSI). Results show that a score of 11 on the BAI is associated with the upper range of mild anxiety on the NSI with excellent sensitivity (0.9394) and good specificity (0.6333).	Clinical veteran population ($n = 308$) and 95.8% met criteria for concussion after TBI testing ($n = 364$).	Palmer and Palmer, 2021
Millon Clinical Multiaxial Inventory (MCMI)	Sensitivity and specificity of detecting malingering using the MCMI improve when appropriate cutoffs are applied in TBI populations. A cutoff for disclosure ≥ 67, desirability ≤ 54, and debasement ≥ 71, yield 4% false positive error rate and sensitivity of 47% for disclosure, 55% for debasement and 51% for desirability. This increases accuracy of classing half of malingers and only misclassifying 4% of non-malingerers.	Participants diagnosed with TBI ($n = 108$).	Aguerrevere et al., 2011
Minnesota Multiphasic Personality Inventory, Second Edition (MMPI-2)	Determining appropriate cutoffs for the MMPI-2 to optimize the accurate detection of malingering in TBI and other clinical populations. The results show that a Tscore cutoff of >89 in the FBS-r validity scale provides 48% sensitivity for malingers and 96% specificity TBI participants that passed validity measures.	Clinical population ($n = 147$). Participants diagnosed with TBI ($n = 59$).	Schroeder et al., 2012

poorer functioning in different domains, including academic performance, community engagement, interpersonal behavior, emotional state, and cognitive processing (Wade et al., 2016). Sariaslan et al. (2016) found that the risks of disability pension and psychiatric inpatient hospitalization were increased by 106 and 92%, respectively, for individuals who had experienced moderate to severe TBI during their childhood, compared with their unaffected siblings. Another study indicated that children who sustained a severe TBI during childhood displayed impairments in adaptive functioning, based on neuropsychological tests and interviews, 6.9 years post-injury (Tomar et al., 2018). These children displayed deficits in fluid reasoning and processing speed, which predicted risk of poorer outcomes in adulthood. Deficiencies in fluid reasoning may hinder an individual's ability to generate solutions and adapt their thinking to navigate daily problems. At the same time, a decrease in processing speed may interfere with daily tasks like interpreting verbal orders or dealing with the demands of a rapid work environment (Treble-Barna et al., 2017). Jones et al. (2018) found that predictors of poor cognitive function in children 12 months post-injury include low socioeconomic status, male gender, living in rural areas, and having experienced a non-accidental injury.

Within 1 month post-injury, children with mild TBI experienced minimal changes in cognitive recovery and quality-of-life (QoL) (Jones et al., 2018). However, by the 6-month mark, there was observable progress in behavioral adjustment, reflecting improvements from baseline. Similarly, 12 months post-injury, children displayed significant cognitive, behavioral, and QoL improvements.

Studies on moderate-to-severe TBI tend to be grouped together. Kennedy et al. (2022) found that older age at the time of trauma correlated with increased mortality and unfavorable overall recovery in children with moderate-to-severe TBI at 6 months post-injury. However, other studies have distinguished the differences between moderate and severe TBI. Those with severe TBI at the 6-month mark show a deterioration in the ability to copy or memorize complex visual materials, suggesting an increased susceptibility to challenging perceptual tasks (Recla et al., 2013). At 24 months post-injury, children with moderate TBI often face difficulties with short and long-term memory in both verbal and visual domains (Catroppa and Anderson, 2007). Whereas, those with severe TBI functioning worsened during the first year, as shown by their accelerated growth curves, indicating an increased presence of executive function dysfunction, specifically related to emotional control, inhibition, and working memory (Keenan et al., 2021). Severe TBI symptoms also displayed a secondary worsening at 24 months.

> TBI presents with considerable heterogeneity across different individuals, as factors such as the severity of the injury, location of brain damage, age, sex, and pre-existing health conditions can all influence the manifestation and outcome of the injury, leading to highly variable outcomes (Walker et al., 2018).

Studies have found that TBIs during adolescence may be associated with more difficulties in recovery than in young children and adults because adolescence is known as a critical window for plasticity, substantial maturation, and growth (Mulligan et al., 2021). During adolescence, cortical structures undergo extensive remodeling through the process of synaptic pruning, corresponding to a decrease in cortical gray matter, acceleration of myelination of axons, increased axon density, and increased white matter volume. These changes allow the acquisition of higher cognitive functions, such as improved cognitive control, enhanced behavioral regulation, and better social cognition (Mulligan et al., 2021). The development of social skills during adolescence is critical for group membership and connection to others, which can significantly impact psychological wellbeing (Di Battista et al., 2014; Mulligan et al., 2021).

Because adolescence represents a crucial stage in brain development and maturation, any disruption to this process may

have far-reaching consequences beyond the initial injury phase, leading to lasting impairment. The long-term effects of adolescent mTBI can involve attention and executive function deficits (Gutiérrez-Ruiz et al., 2022). Gutiérrez-Ruiz et al. (2022) found that adolescents with mTBI showed lower cognitive processing speeds and a decreased capacity for selective and sustained attentional tasks. These adolescents also showed an increase in symptoms related to anxiety, depression, withdrawal, and social issues (Gutiérrez-Ruiz et al., 2022). Adolescents with moderate or severe TBI experience continuous and significant declines in overall quality of life due to the impact of TBI on important domains of life, such as school, career opportunities, work functioning, and social interactions (Mulligan et al., 2021). Moreover, alterations in self-perception were observed, encompassing feelings of inferior intelligence and self-consciousness resulting in diminished social identity while increasing their reliance on others. These findings are similar to research on adult survivors of adolescent TBI, who reported "poorer school performance, greater employment difficulties, poor health-related quality of life (HRQoL), and increased risk of mental health problems" (Di Battista et al., 2014, p. 1).

With TBI recovery in adolescents, Rivara et al. (2011) found that those with mild TBI, 3 months post-injury, showed a minor decline in quality-of-life (QoL). During follow up periods, at 12 and 24 months, these patients exhibited lower QoL scores, reaching statistical significance without reaching clinically significant levels. In another study, Ryan et al. (2015a) found that adolescents with mild TBI at 12 months post-injury exhibited minimal issues with social functioning, and their social abilities remained relatively stable over time. These studies suggest that sustaining mild TBI during adolescence results in more favorable recovery outcomes.

Adolescents with moderate-to-severe TBI, 3 months post-injury, showed a significant reduction in the range of activities, social and community-based, that they could engage in. Additionally, they experienced a reduction in their communication and self-care abilities compared to their initial baseline measurements (Rivara et al., 2011). At 12 months post-injury, adolescents with moderate-to-severe TBI showed improvement in the range of activities they could participate in, although significant impairments still persisted. Additionally, at the 24- month mark, there were some minor improvements; however, their Pediatric Quality of Life Inventory scores remained significantly lower when compared to baseline. Upon further observation, these patients' communication and self-care abilities showed no significant improvements (Rivara et al., 2011). Between the 12- and 24-month post-injury period, adolescents with severe TBI experienced a significant increase in social problems (Ryan et al., 2015a).

The factors associated with the healing trajectory for TBIs in adulthood include patient characteristics, such as a history of recurrent mTBIs, younger age, and greater educational attainment (List et al., 2015; Rabinowitz et al., 2018). List et al. (2015) found that adult patients with recurrent TBIs had a higher prevalence of cognitive deficits for those who had sustained three or more mTBIs compared with those who had experienced 1 to 2 mTBIs.

Recurrent mTBIs are seen as a risk factor that contributes to the development of dementia later in life. In some individuals, mTBI may even lead to an earlier onset of Alzheimer's disease (AD). The increased risk of AD may be due to accelerated neurodegeneration caused by TBI-induced neurotoxic processes, inflammatory processes, and the accumulation of hyperphosphorylated tau. However, younger adult age has been found to be correlated with more rapid improvement than older age (Rabinowitz et al., 2018). Education has also been indicated as a moderating factor in post-injury function. Rabinowitz et al. (2018) found that participants' education level had a significant effect on their processing speed (PS), executive function (EF), and verbal learning (VL) but did not have an impact on their recovery trajectory. In comparison, younger age was correlated with better recovery of both simple and complex PS and EF. This may indicate that age is a protective factor in the recovery of TBI. However, recurrent injury leads to dose-dependent cortical thinning, resulting in detrimental effects on cognitive function that can contribute to the development of AD (List et al., 2015).

With TBI recovery in adults, Othman et al. (2022) found that 19.2% of adults with mild TBI, 3 months post-injury, showed cognitive impairment, while 19.2% exhibited neuropsychiatric manifestations. At 6 months post-injury, patients continued to experience persistent cognitive impairment, while the remaining majority showed signs of recovery. In another study, Scholten et al. (2015) found that at 6 and 7 months post-injury, adults with mild TBI exhibited significantly more favorable outcomes in various domains, such as Physical Component Summary (PCS) scores, physical functioning, role physical, social functioning, and role emotional. At 12 months post-injury, patients demonstrated outcomes that were similar to population norms, indicating a substantial level of recovery.

In adults with moderate TBI, 3 months post-injury, 39.3% of patients presented cognitive impairment, while 25% exhibited neuropsychiatric manifestations (Othman et al., 2022). At 6 months post-injury, no patients exhibited persistent cognitive impairment or neuropsychiatric manifestations. However, the study by Scholten et al. (2015) found that functional outcome and Health-Related Quality of Life (HRQL) were notably lower when compared to the outcomes observed after mild TBI. Notably, when examined 12 months post-injury, patients with moderate TBI scored higher on physical functioning, general health, and vitality on the Short-Form Health Survey (SF-36; reflecting physical, mental, and social functioning) than those with mild TBI. However, Glasgow Outcome Scale Extended (GOSE) scores were significantly lower than for those with mild TBI (Scholten et al., 2015).

Wilkins et al. (2019) found that in adults with severe TBI, 3–6 months post injury, 43% of survivors demonstrate improvement in their outcome, transitioning from unfavorable to favorable. Interestingly, 6 months post-injury, severe TBI patients scored higher in nearly all SF-36 domains and reported higher PQoL scores than moderate TBI (Scholten et al., 2015). This could be attributed to survivors of severe injuries perceiving some of their challenges as less difficult or their gratitude for being alive potentially outweighing concerns about their functional abilities. However, their functional outcome and HRQL were notably lower compared to the outcomes observed after mild TBI (Scholten et al., 2015). Twelve months post-injury, patients with severe TBI had significantly lower outcomes than mild TBI in the SF-36 domains

of PCS, physical functioning, role physical, social functioning, and role emotional. Additionally, GOSE was significantly lower for severe TBI than mild TBI (Scholten et al., 2015). This observation aligns with the study by Wilkins et al. (2019), which reported that 38% of patients with severe TBI improved from unfavorable to favorable outcomes from 12 to 24 months.

When examining traumatic brain injuries (TBIs) in late adulthood, it becomes apparent that the healing trajectory is worse. The majority of the literature indicates an increase in mortality rates and poor functional outcomes. Elderly adults experience worse outcomes after TBIs due to their age, which is found to be an independent risk factor (Prasad et al., 2018; Toth et al., 2021). As individuals age, the brain undergoes atrophy, which leads to an increase in the distance between the brain and skull, making the dural vessels more susceptible to shearing damage. Many elderly patients may live with medical conditions that are masked by TBIs, and their decreased cerebral reserve makes them more vulnerable to minor injuries (Prasad et al., 2018). For instance, if an individual with advanced dementia suffers a head injury, it can lead to cognitive impairments that may prevent independent living. There is a lack of clear guidelines for the treatment of elderly TBI, and the existing guidelines are primarily based on studies of younger adults. This contributes to higher mortality rates and poor functional outcomes in elderly patients. Prasad et al. (2018) further found that, compared with younger patients, elderly patients typically have more extended rehabilitation stays, higher total rehabilitation costs, and a lower rate of improvement in functional measures. Aging and TBI also increase the risk of developing cerebral microbleeds (CMBs). Toth et al. (2021) found that both aging and TBIs can cause CMBs through mechanisms such as cerebrovascular oxidative stress, matrix metalloproteinase activation, and changes in the cerebrovascular wall. CMBs impact the healing trajectory of the elderly because they may lead to "cognitive impairments, psychiatric disorders, and gait dysfunction" (p. 1).

The prognosis for recovery following traumatic brain injury in older adults is generally poor, with substantial evidence indicating high mortality rates and limited functional independence. TBI recovery in older adults shows that those with mild TBI, 3 months post injury, exhibited lower cognitive functioning and performed worse on neuropsychological tests compared to non-injured peers (Hume et al., 2023). At 6 months post-injury, 14% of older adult patients with mild TBI died (Utomo et al., 2009). Thompson et al. (2020) compared older and younger adults with mild TBI, finding that from 1 week to 1 year post-injury, older adults consistently reported poorer overall physical Health-Related Quality of Life (HRQOL) than their younger counterparts.

Older adults with moderate TBI, 3 months post-injury, experience significantly poorer functional health status, with an average Glasgow Outcome Scale Extended (GOSE) score of 5.1, indicating a greater degree of disability following a moderate TBI compared to younger adults (Thompson et al., 2020). At 6 months post-injury, 47.8% of patients with moderate TBI died (Utomo et al., 2009). One-year post-injury, older adults with moderate TBI continued to report an ongoing average of 3.9 symptoms out of 17 symptoms assessed, with a higher likelihood of experiencing balance and coordination issues (Thompson et al., 2020).

Older adults with severe TBI, 6 months post-injury, with a Glasgow score of <9 exhibited unfavorable outcomes, with a significant mortality rate of 83.3% (Utomo et al., 2009). Similarly, Maiden et al. (2020) found that 6 months post-injury, 85% had died, 47% were living dependently, and 6% had recovered to functional independence. By 12 months post injury, 86.3% had died, 6.4% were living dependently, and 7.3% had recovered to functional independence. Overall, the data reveals that older adults with severe TBI face a substantial risk of death, with only a minority regaining functional independence. The following figure (Figure 1) shows children, adolescent, adult, and elderly TBI risk factors.

Phenomenology of TBIs

Phenomenological studies of TBI healing progression can provide valuable insights into the subjective experiences of individuals with TBI and the factors that shape their recovery journey. By understanding the individual's perspective on their recovery, healthcare professionals can better tailor their treatment approaches and support the individual in their efforts to recover and return to their everyday lives.

Many phenomenological studies of TBI have interviewed patients during their recovery to assess their functional outcomes and wellbeing over time. Wellbeing is typically categorized as psychological, physical, and social, but there is often overlap between these categories in the literature on TBI healing progression.

Visser et al. (2021) conducted a study examining patients' wellbeing after injury, from their experiences in the emergency room to discharge and rehabilitation. Patients who were severely injured reported feeling a fear of dying while being treated in the ambulance and emergency room. For instance, one patient (female, >16 years) feared she was going to die after seeing blood spouting from her leg, thinking it was arterial bleeding (Visser et al., 2021). Patients who were sedated, unconscious, or experiencing post-traumatic amnesia during treatment often reported feelings of confusion and anxiety about the events of their injury. The realization that they had survived the injury often came to patients during hospitalization and recovery, and this realization was frequently accompanied by a fear of permanent physical limitation, replacing the earlier fear of dying. These findings highlight the initial emotional turmoil and evolving fears faced by patients after severe injuries.

Many patients reported experiencing symptoms of acute stress disorder (ASD) during hospitalization and post-traumatic stress disorder (PTSD) during rehabilitation. Stenberg et al. (2022) followed up with patients 1 and 7 years after TBI and found that wellbeing resulted from adaptation to a recovered or changed life situation. Those with moderate to severe disabilities reported poor wellbeing because adaptation was an ongoing process. However, patients reported that adaptation and wellbeing were facilitated by factors such as leading a purposeful daily life, maintaining an optimistic perspective, and employing adaptive strategies, such as applying knowledge gained from previous hardships. For instance, when asked about the ability to adapt, one patient (Female, 36 years) expressed that despite her permanent injuries, she focused on choosing to be positive and appreciating the good things in life rather than being sad about the negative things (Stenberg et al.,

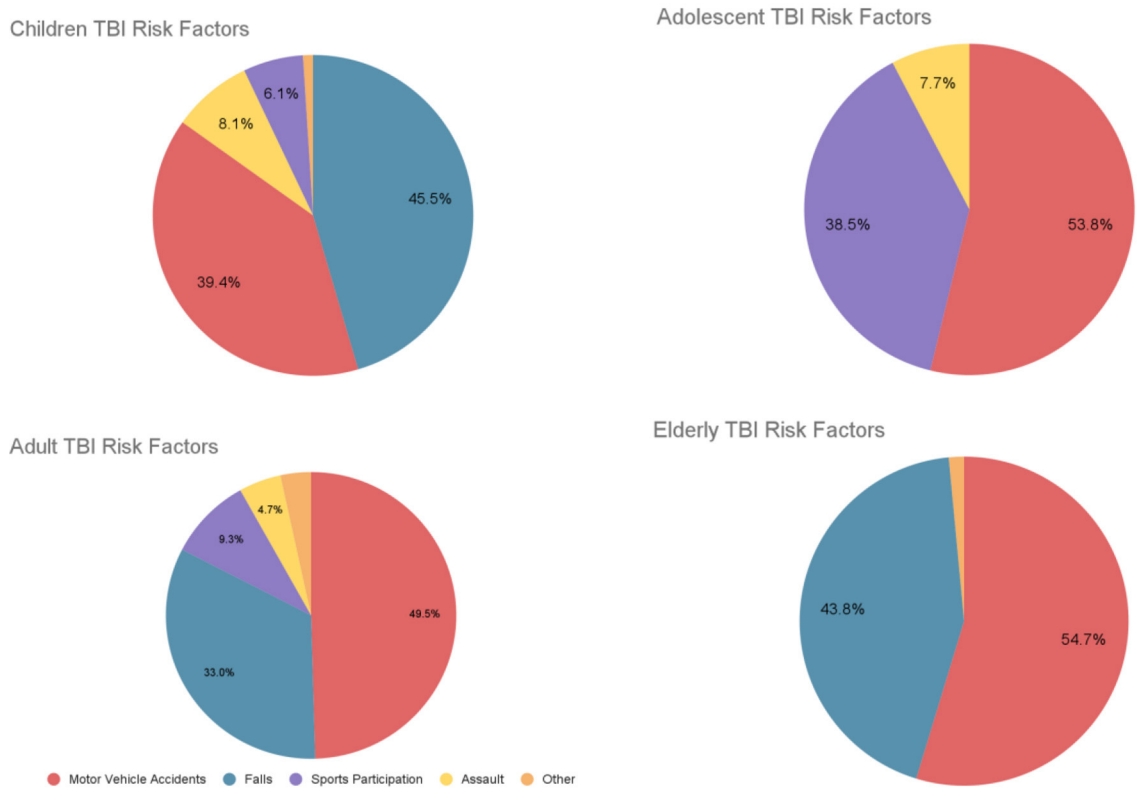

FIGURE 1
Children, adolescents, adults, and elderly TBI risk factors. Based on data from Keenan et al. (2021), Mulligan et al. (2021), Scholten et al. (2015), and Prasad et al. (2018).

2022). Developing resilience and a positive outlook helped mitigate the negative emotional impact of TBIs in patients' lives.

Experiences related to physical function also contributed to patients' wellbeing. Visser et al. (2021) found that patients often reported that the time needed for recovery was much longer than they anticipated. The desire to feel autonomous rather than helpless often motivated severely injured patients to push through physical limitations during rehabilitation. Stenberg et al. (2022) found that patients with severe TBI reported suffering from life long limitations that impact their health and wellbeing. Overcoming obstacles such as the denial of one's disabilities, feelings of guilt, shame, loneliness, and isolation, and avoidant behavior were all described as necessary for adaptation and wellbeing by severely injured patients. For instance, when asked about difficulties in adapting, one patient (Male, 27 years) expressed increasing depression and frustration due to the persistent impact of his injuries on his life (Stenberg et al., 2022). These experiences reveal the persistent challenges and emotional struggles that accompany physical recovery.

Social support is another critical aspect of TBI recovery, as it is known to improve mental health and overall wellbeing. Visser et al. (2021) found that while it was challenging to rely on others, patients were thankful for the assistance they received from loved ones. In addition, patients believed that their friends' and family's support could aid their recovery. Stenberg et al. (2022) found that living with a severe disability impacted patients' social wellbeing. Patients coping with a severe disability described it as frustrating and leading to loneliness in daily life, as it resulted in exclusion from work and social networks, and the inability to participate in leisure activities. For instance, when asked about living with a disability, one patient (Male, 57 years) described feeling extremely lonely and frustrated by his inability to communicate and participate in activities, ultimately accepting his situation with difficulty (Stenberg et al., 2022). Social support is crucial in mitigating the isolation and emotional distress experienced by TBI patients.

Defense or deficit?

Phenomenological studies help "humanize" TBI accounts, especially in such reviews as this. The difficulties mentioned in previous examples, in combination with cognitive deficits summarized throughout lead to another important consideration for all neuropsychologists, especially when involved in therapeutic intervention (directly or indirectly). This is the development of the knowledge and skills necessary to help determine whether the patient's presentation is a psychological defense or deficit. These defenses can be a false positive, masking a cognitive deficit, or the cognitive deficit may mimic a defense. The following are some examples where defenses and deficits may be confused:

1. Anosagnosia, or a lack of insight into ones own impairments, may be confused with denial.
2. Executive dysfunction may lead to misattribution of blame, disinhibition and lack of self insight which could be confused with projection, acting out or displacement.
3. Rationalization may also stem from impaired judgment due to frontal compromise, as opposed to a personality type, or emotional reaction.
4. Repression or lack of details related to PTSD could be confused with significant reductions in memory processes related to TBI.
5. Reaction formation or when a polarization of belief occurs, specifically one that was opposite to what the individual previously identified with could arise from deficits in memory, and emotion related systems.

In these instances, a neuropsychological evaluation will play an important role for clinical judgment. TBI victims in inpatient units are typically physically and emotionally vulnerable, creating an environment conducive to the expression of defenses. Outpatients will likely be easier to determine, given discharge is normally associated with a level of stability that improves the likelihood of a comprehensive evaluation, consistency and increased number of sessions.

Treatment and rehabilitation

Once the patient has been assessed, and deficits ascertained, what can be done? Treatment and rehabilitation for TBI is dependent on the recovery stage of the patient. In the acute stage, in the hours immediately following injury, the main focus of treatment is to stabilize the patient and focus on preventing further injury. Typically, treatment is carried out at an intensive care unit, followed by a neurosurgical ward. For chronic stages of recovery, rehabilitation is the main treatment, and a variety of rehabilitation and treatment protocols exist.

The Rancho Los Amigos Scale-Revised (RLAS-R) is an assessment tool used to describe the cognitive and behavioral patterns found in brain injury patients as they recover from injury. The scale consists of ten levels, with the first level representing the lowest level of functioning, and the tenth level representing the highest. As a patient progresses through higher levels, they demonstrate an improved capacity toward achieving greater independence. Overall, the scale helps facilitate communication among treating healthcare professionals and aids in treatment planning; individualized treatment interventions can be administered depending on the patient's level of functioning and impairments. While individuals move through the different levels in a sequential pattern, the amount of time spent in each level and the maximum level achieved varies by individual. Additionally, levels can be skipped during their recovery, and behaviors can overlap between two different levels. The following table (Table 5) shows the RLAS-R.

The RLAS-R is typically paired with the GCS to assist in determining the TBI patient's responsiveness. However, unlike the GCS, the RLAS-R is usually used throughout the recovery period, and is not limited to the initial assessment. Earlier screening of cognitive function is important for the prediction of recovery outcomes and facilitates rehabilitation planning.

The administration of the RLAS-R can also be used in conjunction with the Montreal Cognitive Assessment (MoCA). The MoCA is a cognitive assessment that is administered in roughly 10 min and scored on a maximum of 30 points. The domains of function measured includes visuospatial/executive functioning, memory, language, attention, concentration, working memory, and orientation. Individuals with mild and moderate TBI typically have better performances on the MoCA than those with severe TBI (de Guise et al., 2013), and the MoCA can reliably detect impairment in mild TBI and differentiate cognitive disabilities between mild to severe TBI (Mishra et al., 2020).

Once a patient is medically stable following the TBI, they may be transferred to a subacute rehabilitation unit of a medical center, or to an independent rehabilitation hospital. Typically, a multidisciplinary approach is utilized to optimize patient outcomes. The target of rehabilitation treatment will depend on the injury sustained and the associated neurological deficits; as such, treatment may include (but not limited to) physiotherapy, speech and language therapy, cognitive rehabilitation therapy, and occupational therapy.

Cognitive rehabilitation typically consists of training various aspects of cognitive functioning, including learning and memory, visual attention and auditory attention, psychomotor function, and executive functioning. Restorative interventions aim to restore impaired functionality, while compensatory interventions (i.e., cognitive remediation) assist in the development of strategies to minimize the functional impact of the impairment. Neuropsychologists can assess for TBI-induced deficits utilizing a wide-variety of assessment tools, and can prescribe various forms of training to restore or remediate cognitive functioning.

Attention-related difficulties are common among individuals with TBI and can manifest in a variety of ways. Computer-mediated tasks designed to retrain attention can lead to gains on the trained tasks with generalization to similar cognitive measures. However, the results do not always generalize to everyday attentional behavior. Engaging in metacognition, which includes self-reflective capacities and an increase in self-awareness and self-monitoring, has been found to compensate for attentional problems in adults (Ponsford et al., 2014). Metacognitive can also help with problem solving in adults (Tate et al., 2014).

Memory problems can be compensated for in various ways; internal memory strategies, such as mnemonics, visual imagery, and self-instructional methods have been shown to enhance performance on neuropsychological tests. Other helpful memory supports include diaries, notebooks, smart phones, and electronic calendars. Additionally, self-instructional methods that aim to enhance the individual's understanding of manifestations of their memory problems have been shown to improve prospective memory (Velikonja et al., 2014).

TBI often results in communication disturbances that can lead to impaired social competence for both children and adults. Social communication training in group formats has been found to be an effective intervention for individuals 6–24 months post injury. Such training can incorporate everyday communication with partners, and individuals are encouraged to practice the skills

TABLE 5 Rancho Los Amigos (revised) (Hagen et al., 1972; Lin and Wroten, 2023).

Level	Cognitive response/need of assistance	Clinical features
Level I	No response/total assistance	No response to external stimuli
Level II	Generalized response/total assistance	Respond inconsistently and non-purposefully to external stimuli. Responses are often the same regardless of the stimulus applied.
Level III	Localized response/total assistance	Respond inconsistently and specifically to external stimuli. Responses are directly related to the stimulus. Tend to be more responsive to familiar people (friends and family) than to strangers
Level IV	Confused and agitated/maxassist	In a hyperactive state with bizarre and non-purposeful behavior. Demonstrate agitated behavior that originates more from internal confusion than the external environment
Level V	Confused, inappropriate non agitated/max assist	Show an increase in consistency with following and responding to simple commands, their responses are non-purposeful and random to more complex commands. Behavior and verbalization are often inappropriate, and the patient can appear confused and often confabulates. Can perform an action or task if it is first modeled or demonstrated for them, they do not yet initiate tasks on their own. Memory is severely impaired and learning new information is difficult. Can show agitation to unpleasant external stimuli
Level VI	Confused, appropriate/mod assist	Able to follow simple commands consistently. Able to retain learning for familiar tasks they performed pre-injury (brushing teeth, washing face) but are unable to retain learning for new tasks. Demonstrate an increased awareness of self, situation, and their environment but are unaware of any specific impairments and safety concerns. Responses may be incorrect secondary to memory impairments but appropriate to the situation
Level VII	Automatic, appropriate/min assist for ADLs	Oriented in familiar settings. Able to perform a daily routine automatically with absent to minimal confusion Demonstrate carry over for new tasks and learning in addition to familiar tasks. Can be superficially aware of diagnosis but unaware of specific impairments. Continue to demonstrate a lack of insight, decreased judgment and safety awareness. Beginning to show interest in social and recreational activities in structured settings. Require at least minimal supervision for learning and safety purposes
Level VIII	Purposeful, appropriate/stand by assist	Consistently oriented to person, place, and time. Can independently carry out familiar tasks in a non-distracting environment. Beginning to show awareness of their specific impairments and how they interfere with tasks, but they still require stand by assistance with compensatory skills. Able to use assistive memory devices to recall a daily schedule. Acknowledge other people's emotional states and require only minimal assistance to respond appropriately. Demonstrate improvement of memory and ability to consolidate past and future event. Often depressed, irritable, and demonstrate a low threshold to rustration
Level IX	Purposeful, appropriate/stand by assist on request	Able to shift between different tasks and complete them independently. Aware of and acknowledge their impairments when they interfere with tasks. Able to use compensatory strategies to cope. Able to independently anticipate obstacles that may arise secondary to any lingering impairments. Able to consider the consequences of actions and decisions with assistance. Continue to demonstrate depression and low frustration thresholds
Level X	Purposeful, appropriate/modified independent	Able to multitask in many different environments with extra time for task completion or devices to assist. Able to create their own methods and tools for memory retention. Can independently anticipate obstacles that may occur as a result of their impairments and take corrective actions. Able to independently make decisions and act appropriately but may require more time or compensatory strategies. May still demonstrate intermittent periods of depression and a lowered threshold for frustration when under stress. Able to appropriately interact with others in social situations

they learn beyond the period of training. Social communication interventions can be provided in the natural environment of the person's everyday life (Togher et al., 2014).

Several non-invasive brain stimulation technologies have been developed that can lead to reduced symptomology for TBI patients. The most common technologies include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). tDCS has been shown to reduce TBI-associated depression, tinnitus, neglect, memory deficits, and attention disorders (Dhaliwal et al., 2015). Repetitive transcranial magnetic stimulation (rTMS) is another non-invasive, easily operated treatment that has been shown to improve depression and increase cognitive function after TBI (Neville et al., 2015).

Virtual Reality (VR) has been shown to be an effective rehabilitation tool and can function both as an assessment instrument and as a therapeutic intervention. Dahdah et al. (2017) found that VR can enhance executive functions and information processing in the sub-acute phase of TBI. It has also been used for attention training in severe TBI (Dvorkin et al., 2013), and has been effective in addressing and treating balance deficits (Cuthbert et al., 2014).

Digital brain games overall have yielded mixed results. Some however have demonstrated to efficiently improve cognition among individuals with TBI. BrainHQ is a common and frequently used online platform in which users can play games to train their memory, attention, cognitive speed, interpersonal skills,

intelligence, and navigation. Research has found that BrainHQ training can result in both objective and subjective improvements on cognitive measures, which correlates with changes in functional connectivity between the DMN and other resting-state networks in adults with chronic TBI (Lindsey et al., 2022).

Functional electrical stimulation (FES) refers to a process whereby a low-frequency pulse current is used to stimulate limb or organ dysfunction, thereby replacing or correcting lost function in limbs and organs. FES has been shown to have a positive effect on a TBI patient suffering from dysphagia (Calabrò et al., 2016). Though this study only included one individual, the results demonstrated that FES led to significantly improved swallowing functionality in this patient, who could eventually eat solid food safely after the treatment. This suggests that FES may constitute a promising effective treatment for improving lost functionality after TBI, and future research should continue to investigate its potential therapeutic effects with larger sample sizes. There is also evidence that FES can lead to cortical reorganization among individuals with TBI. Milosevic et al. (2021) found that FES treatment led to cortical reorganization and motor improvements in a male participant with chronic TBI suffering from mild motor impairment affecting his right upper-limb. Widespread changes were observed in the motor, premotor, sensory, and parietal cortices in both contralateral and ipsilateral hemispheres and his drawing test performance showed improvements after the intervention and during 3-month follow ups. Again, while this study only included one individual, the results suggest that FES may be an effective tool to improve motor functionality and elicit cortical re-organization and highlight the necessity for future research with larger cohorts of patients.

Hyperbaric Oxygen Therapy (HBOT) refers to the inhalation of 100% at higher than atmospheric pressure and has been used as a treatment for a variety of neurological conditions. HBOT can lead to greatly improved symptomology and a reduction in TBI-related cognitive deficits (Harch et al., 2012). In severe TBI, HBOT has been shown to reduce mortality and enhance functional outcomes in both adults (Lv et al., 2011) and children (Prakash et al., 2012). There is also evidence that HBOT may suppress activation of inflammation signals which TBI induces (Meng et al., 2016). However, it must be noted that despite the published literature supporting HBOT's efficacy for TBI, there have been limited double-blind placebo-controlled trials, and thus HBOT is not an FDA-approved therapy for TBI.

Severe TBI can lead to cerebral edema, which can precipitate intracranial hypertension. The treatment of cerebral edema involves cerebrospinal fluid (CSF) drainage, administration of osmolar agents, and/or craniectomy. The prevention of the development of severe oedema can be targeted by emerging treatments such as glibenclamide, which selectively acts on specific ion channel openings in the brain that can prevent the build-up of fluid (Blennow et al., 2016).

Future considerations

Future research on traumatic brain injury (TBI) should prioritize the development of multidimensional outcome assessments to more accurately capture individual impairments and establish precise prognostic endpoints. Traditional global or unidimensional instruments may not fully capture the nuances of TBI-related disabilities. Cognitive impairments and mental health outcomes distinguish between patients with TBI on different levels of disability severity. Cognitive impairment often distinguishes between those with moderate and severe disabilities, while adverse mental health outcomes differentiate patients with higher levels of functional outcomes. Multidimensional outcome assessment can utilize unidimensional instruments such as the Rivermead Post-Concussion Symptoms Questionnaire by reconfiguring a general factor of severity of symptoms into core dimensions of psychopathology (e.g., internalizing factors, somatic symptoms) (Nelson et al., 2021). The individual impact of TBI is inextricably related to individual factors (e.g., preinjury mental health, coping skills), as well as the larger socioeconomic context of access to healthcare. Future studies warrant sample cohorts that are large and heterogeneous in order to distinguish factors and contribute toward a multifactorial (bio-psycho-socio-ecological) model of TBI. The multifactorial model, encompassing biological, psychological, interpersonal, and contextual dynamics, clarifies the relationship between individual and socio-economic determinants of health. This model views health as a dynamic interaction of various systems evolving over time. Following a TBI, biological responses like immune system activation shift alongside changes in interpersonal and psychological dynamics. For instance, in the acute phase, biological factors such as inflammation may dominate, while psychological factors like coping strategies become central during rehabilitation (Lehman et al., 2017). Interpersonal dynamics, such as family support, also play a pivotal role throughout the recovery process.

Neuropsychological research should continue distinguishing the efficacy of particular assessments in distinct contexts (e.g.. sex, education, culture, age, etc.). This promotes a more effective selection of batteries that can be tailored to patients. It will also help direct novices in the field in knowing what variables to pay attention to. In addition, approaching TBIs from a neurophenomenological approach may be greatly beneficial. For instance, in major traumatic brain injuries, global dysfunction (e.g., PTA) undergoes a particular temporal sequence toward recovery. This sequence will vary depending on individual differences, yet it is also possible for there to be underlying commonalities more deeply embedded in the brains organic recovery process. A potential sequence may be reflected in a temporospatial model that tracks the development and maturation of emotion and thoughts (Chan et al., 2022). A more nuanced understanding of this sequence may yield important results that may enrich treatment.

Research on TBI should also increasingly address the chronic nature of TBI symptoms given that TBI symptoms can persist or worsen over time and that a majority of moderate to severe TBI patients experience a decline in functioning and an estimated 20 percent die within 5 years of injury (Whiteneck et al., 2018). An individual's functional outcomes at 2 and 5 years after an injury are greatly influenced by their functional status at the first year. However, several factors, such as age, race, payor source (referring to the source of funding for healthcare expenses), length of rehabilitation stay, and cognitive and motor scores, also have a significant impact on how their condition progresses over time (Dams-O'Connor et al., 2020). Current TBI care in the USA frequently fails to meet the needs of individuals,

families, and communities impacted by TBI (National Academies of Sciences, 2022). Long-term problems can arise beyond the period of post-acute care: fatigue, sleep disturbance, cognitive impairments affecting memory, attention, and executive function, anxiety, and depression, which can affect individuals' ability to work, study, and drive for at least 5–10 years post-injury (Maas et al., 2022). Although international guidelines for treatment of cognitive and communication impairments have been updated in 2022, more large-scale controlled studies are required to validate new interventions (Bayley et al., 2023).

Furthermore, future research should explore the prevalence and long-term effects of post concussion-like symptoms in patients with different types of injuries. Post-concussion-like symptoms are common among all injury patients, and not just those with head injuries. Understanding the risk factors for developing post-concussion symptoms, such as low educational level, road traffic accidents, chronic diseases, and hospitalization, is also important for early detection and prevention (van der Vlegel et al., 2021). Further studies should also investigate the impact and treatment of post-concussion-like symptoms on the quality of life of patients, healthcare utilization, and return to work rates, as these factors can inform the development of supportive care programs.

The use of biomarkers in classifying injury severity of TBI shows a promising path toward identifying specific patient groups related to disease endotypes. Recent research has assessed certain endotypes (e.g., pH, lactate, blood glucose, and platelet count) (Åkerlund et al., 2022), which may correlate with established measures of TBI impact such as the Glasgow Coma Scale score and degree of metabolic derangement. Other circulating biomarkers like amyloid beta (Hossain et al., 2020) and heart fatty acid binding protein (Lagerstedt et al., 2020) are also being studied to be able to categorize subgroups of TBI patients with different inflammatory endotypes or detect the presence of autoantibodies against brain and extracranial antigens (Maas et al., 2022). As these biomarkers may reflect the body's inflammatory response post-injury, clinicians can more appropriately select and implement anti-inflammatory and immunomodulatory therapies with this data. Future identification of new biomarkers will involve advanced analytic techniques, including artificial intelligence and machine learning, and may help refine important medical decisions throughout the treatment and rehabilitation process. The use of fMRI (Madhavan et al., 2019) and MR spectroscopy (Nadel et al., 2021) as research techniques show promise as future clinical tools for assessing TBI patients. Advanced MRI techniques in combination with volumetric analyses (Stein et al., 2021) have demonstrated increased sensitivity to detecting specific injuries, e.g., traumatic axonal injury, which would typically not be detectable by visual inspection. For mTBI patients, such injuries may not present on CT imagery but are relevant for both persistent post-concussion symptoms and long-term disability. There is also an increasing interest in utilizing MRI to assess the chronic phase of TBI because brain injury biomarkers identified by MRI techniques may predict late brain volume loss and reflect accelerated brain aging (Gan et al., 2021; Yin et al., 2019).

While the field of neurorehabilitation is growing, there is still a lack of support concerning what combinations of treatments may be best depending on the type and severity of TBI. Moreover, the use of computerized interventions has also been on the rise, yet research appears to be mixed. Further specificity as to how these differ from each other may lead to the development of more efficacious programs. Beyond programs focused on cognitive restoration, progress on the development of new compensatory strategies have also appeared to stagnate. It will be beneficial for the development of new strategies considering how much science and technology have advanced (e.g., since birth of ideas such as chunking, visualization or method of the loci). In addition, while individualizing such techniques for everyday experiences is commonly done by practitioners involved with neurorehabilitation, it would be of benefit to identify their efficacy under different contexts. The future of rehabilitation will likely be combined with technological advancements. A deeper examination of roles between clinician and technology will give way to the optimal use of new technologies. An example of this might be the importance of the clinician assisting patients in the translation of skills from virtual brain games to everyday life.

Another route of investigation, more biologically oriented relates to mechanisms underlying the long-term effects of TBI, including the role of neurotoxic processes, inflammatory processes, and the accumulation of hyperphosphorylated tau in the development of dementia and AD. Additionally, more research is needed to understand the psychological effects of TBI, including the prevalence and long-term effects of affective disorders such as anxiety, depression, and PTSD. TBIs can have significant psychological consequences, as they can disrupt the brain's functioning and alter neural pathways involved in emotional regulation. This research may involve longitudinal studies that track individuals with TBIs over an extended period, assessing their psychological wellbeing and identifying risk factors that contribute to the development of affective disorders. By gaining a better understanding of these psychological effects, healthcare professionals can develop more targeted interventions and support systems to improve the overall outcomes and quality of life for individuals with TBIs.

Conclusion

The assessment and treatment of TBIs provides a unique window into the brain's capabilities and vulnerabilities. Similar to how brain lesions provide a deeper understanding of their corresponding functions, TBIs may be a lens into the underlying processes of cognition, emotion and personality. TBIs are a multidimensional, complex injuries that can result in a range of physical, cognitive, and emotional deficits. The brain areas most vulnerable to injury are the frontal and temporal cortices leading to deficits in executive functioning, attention, memory, language, and emotional processing. Deficits in processing correlate with impairments in identifying negative emotions, affective disorders such as anxiety, depression, and PTSD. Mild TBI, accounting for the majority of cases, can cause temporary post-concussive symptoms that may resolve within a few months and temporary cognitive symptoms within a few days. However, even a single mTBI or recurrent mTBI can result in the emergence of depressive-like behaviors up to 90 days following the injury. On the other hand, moderate and severe TBIs are more serious and can lead to long-term complications, even death.

The trajectory of healing for TBI varies depending on the developmental stage of the individual. Adolescents who sustain TBI may have more difficulties in recovery than young children and adults due to their critical window for plasticity, substantial maturation, and growth. Several factors influence the healing process of traumatic brain injuries (TBIs) in adults. These factors include patient characteristics like a history of repeated TBIs, younger age, and higher levels of education. Individuals who have experienced multiple TBIs are more likely to have cognitive deficits compared with those who have had fewer incidents. Recurrent TBIs are also associated with an increased risk of developing dementia later in life. In certain cases, mTBI may even accelerate the onset of Alzheimer's disease.

Evolution has left humans with the cognitive ability to generate sophisticated methods for the assessment and treatment of TBIs. Grounded in research, neuropsychological assessments are themselves a product of evolutionary necessity, offsetting our brains vulnerability by providing critical and nuanced information that can be used practically. At its core, neuropsychological results provide (1) viable predictions on functional outcome that can assist with expectation management, (2) strengths that can be used to compensate for challenges, (3) weaknesses that are specifically targeted for restoration/compensation, and (4) an optimal path for recovery and adaptation.

Author contributions

AC: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. JO: Supervision, Writing – original draft, Writing – review & editing. KN: Writing – original draft. AJ: Writing – original draft. SB: Writing – original draft. RK: Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 17 October 2024
DOI 10.3389/fneur.2024.1453629

OPEN ACCESS

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RECEIVED 24 June 2024
ACCEPTED 27 September 2024
PUBLISHED 17 October 2024

CITATION
Yang Y, Zhu X, Yang T, Fan K, Cheng J and Ma Y (2024) The clinical differences between traumatic and NOS chronic subdural hematoma. *Front. Neurol.* 15:1453629. doi: 10.3389/fneur.2024.1453629

The clinical differences between traumatic and NOS chronic subdural hematoma

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Objective: Chronic subdural hematoma (CSDH) is a common neurologic disorder with increasing incidence, which can be preceded by head trauma or occur in the absence of trauma. In order to deeply understand the clinical characteristics of this disease, we conducted this retrospective study to explore the clinical differences between traumatic and not otherwise specified (NOS) CSDH.

Methods: According to the inclusion and exclusion criteria, 168 traumatic CSDH patients and 133 NOS CSDH patients were recruited from January 2015 to October 2023 in our cohort. The collected data and compared parameters including baseline clinical features and radiological outcomes of hematoma within 24 h of hospital admission, as well as the treatment method and clinical outcome of traumatic and NOS CSDH patients.

Results: Compared to NOS CSDH patients, the average age was younger, epilepsy was more frequent, asymptomatic cases were more common, and the taking of anticoagulants and antiplatelet drugs were rarer in traumatic CSDH patients (all $P < 0.05$). However, no differences were found in the radiological presentations of hematoma at admission, the treatment methods and clinical outcomes of traumatic and NOS CSDH patients (all $P > 0.05$).

Conclusion: Traumatic CSDH patients were more likely to be asymptomatic or have seizures, while NOS CSDH were more common in elder people and in individuals with the history of taking anticoagulants and antiplatelet drugs. The treatment methods and clinical outcomes were similar in traumatic and NOS CSDH patients.

KEYWORDS

chronic subdural hematoma, trauma, clinical characteristics, clinical outcome, burr-hole craniotomy

1 Introduction

Chronic subdural hematoma (CSDH) is a common neurologic disease, which is characterized by the pathological collection of blood and blood breakdown products in the subdural space (1, 2). CSDH is often induced by head trauma via tearing the bridging veins with subsequent bleeding and hematoma creating, but it can also occur without trauma history in about 30%−50% cases (3–5). Apart from trauma, other risk factors that might be related to the onset of CSDH including the use of anticoagulants and antiplatelet drugs, alcohol abuse, cerebrospinal fluid shunts and so on (6, 7). CSDH patients with different inciting events might have various clinical characteristics. Until now, it is unclear

whether there are differences in clinical features and treatment outcomes between traumatic and not otherwise specified (NOS) CSDH patients. Hence, it is of great potential significance to explore the clinical differences between traumatic and NOS CSDH.

CSDH patients can present with variable clinical manifestations including headache, nausea or vomiting, limb weakness, sensory disturbance, seizure, cognitive impairment, and so on (8–11). These symptoms result from the accumulation of blood in subdural space over time, the ongoing processes such as angiogenesis, fibrinolysis and inflammation subsequently, the elevation of intracranial pressure and the compression of brain parenchyma after 4–7 weeks ultimately (9–12). The diagnosis of CSDH is based on the combination of above clinical symptoms and radiological investigation, mostly computed tomography (CT) scan. CT not only reflects the shape, density and volume of the hematoma, but also reveals the natural development of CSDH from a homogeneous type into a laminar, then separated type, and finally be absorbed as a trabecular hematoma (13, 14). The treatment strategy of CSDH consists of surgical evacuation through burr-hole craniotomy, the medication therapy including dexamethasone and atorvastatin, and conservative observation. Surgical treatment is appropriate for patients with impeding, progressive, or severe neurological symptoms, which can obtain a fast neurological improvement via an immediate relief of pressure on the ipsilateral hemisphere (14, 15). Medication therapy is used as an alternative therapy for symptomatic patients, in an attempt to avoid surgery or reduce postoperative recurrence risk (14). Observational therapy is applied to treat asymptomatic patients or patients with mild symptoms. Based on the above mentioned literature, we think it is meaningful to analyze the differences of clinical symptoms, CT results, treatment strategies, and treatment outcomes between traumatic and NOS CSDH patients.

To our knowledge, few studies have identified the clinical differences between traumatic and NOS CSDH. Herein, the present study was conducted to compare parameters including baseline clinical features and radiological outcomes of hematoma, as well as the treatment method and clinical outcome of traumatic and NOS CSDH patients. The aim of this study is to clarify the clinical differences between traumatic and NOS CSDH, and further to provide a theoretical basis for earning more effective treatments and better outcomes.

2 Materials and methods

2.1 Setting

We conducted this retrospective study and collected the clinical data of traumatic and NOS CSDH patients at the General Hospital of Western Theater Command in Chengdu, China. Traumatic CSDH refers to the main symptoms that lead to the hospitalization of patients are closely related to head trauma such as fallen, traffic accidents during the past days or weeks. The main symptoms include persistent headache or dizzy, transient disturbance of consciousness, reduced recent memory, limb weakness, seizure, cognitive impairment, and so on. NOS CSDH refers to patients present as above symptoms, but without the head trauma. The department of neurosurgery in the hospital have professional neurosurgeons and nurses, who are in charge of formulating treatment and care plans for CSDH patients. Ethics committee of the faculty of The General Hospital of Western Theater Command gave permission for this research. All the studying processes were carried out in accordance with the approved guidelines.

2.2 Patients

Traumatic and NOS CSDH patients were recruited from the inpatient service of The General Hospital of Western Theater Command in Chengdu, China. The collected data including complete admission and hospitalization records of all patients with CSDH from January 2015 to October 2023. The inclusion criteria including: (1) Age $\geq$ 18 years. (2) The discharge diagnosis was CSDH. (3) Patients can clearly recall and state the course of disease, especially the course of head trauma event of traumatic CSDH. Patients with following situations were excluded: (1) The admission and hospitalization information was incomplete. (2) Patients cannot recall the course of disease, especially cannot clarify the relation between the onset of CSDH and head trauma. (3) Presence of extracranial injury (such as orthopedic/cardiac/chest/abdominal/pelvis traumatic injury and so on). (4) Pre-existing severe cardiac diseases (such as myocardial ischemia/infarction, heart failure). (5) Combined with liver/renal/lung failure, hematological disease, infection disease, malignancy, and pregnancy.

2.3 Clinical care of patients with CSDH

Once patients arrived at the department of neurosurgery in our hospital, standard treatments and management were carried out immediately. All the CSDH patients received comprehensive neurological evaluation and underwent cranial CT scan subsequently. And, repeat CT scan was conducted when patients showed the indication of clinical deterioration or the sign of intracranial pressure elevation. Moreover, other routine clinical examinations including chest X-Ray, abdomen ultrasound, electrocardiogram and laboratory tests including hematology, urine and feces analysis, lipid, and coagulation profile, multiorgan (cardiac, liver, and renal) function analysis were conducted within 12 h after patients were hospitalized. Once the patient was diagnosed as CSDH, appropriate treatment including surgical hematoma evacuation through burr-hole craniotomy, the medication therapy including dexamethasone/atorvastatin, and conservative observation would be conducted.

2.4 Data collection

All parameters that might be different between traumatic and NOS CSDH according to our existing knowledge and previous literature were analyzed in this study. The collected data including baseline clinical features and radiological outcomes of hematoma within 24 h of hospital admission, as well as the treatment method and clinical outcome of traumatic and NOS CSDH patients.

Baseline clinical features involved demography, main symptoms, initial GCS, mode of trauma and medical history. Radiological outcomes of hematoma included hematoma location, maximum thickness, midline shift, and hematoma volume based on the CT presentation. Treatment methods consisted of borehole drainage, atorvastatin and dexamethasone. And, clinical outcomes were evaluated by neurological function, hospital stays, and total costs.

2.5 Data analysis

Measurement data was expressed as mean values ± standard deviations (M ± SD). Differences between two groups were analyzed by Unpaired *t* test with Welch's correction. Enumeration data was analyzed by Chi-squared test. SPSS version 18.0 software (SPSS Inc., USA) was used to perform the analysis, and two-tailed $P < 0.05$ was considered statistically significant. Photoshop software (Adobe Software, Inc., USA) was used to draw the figure.

3 Results

3.1 Patients selection

All CSDH patients were screened from the inpatient service of The General Hospital of Western Theater Command in Chengdu from January 2015 to October 2023 by using ICD-9 procedural code terminology. CSDH patients were further selected according to the inclusion and exclusion criteria as described in "Materials and Methods" section. At last, 168 traumatic CSDH and 133 NOS CSDH patients were recruited. The selection flowchart was illustrated in Figure 1.

3.2 Traumatic and NOS CSDH patients had different baseline clinical features

Traumatic and NOS CSDH patients had similar gender distribution, but the mean age of the latter was older (65.9 ± 16.3 y vs. 70.8 ± 13.0 y, $P = 0.005$). Traumatic and NOS CSDH patients had similar mean GCS score and severity of illness, but had different main symptoms. Results indicated that epilepsy was more frequent and asymptomatic cases were more common in traumatic CSDH patients compared to NOS CSDH patients (7.7% vs. 3.0% and 15.5% vs. 6.8%, $P < 0.001$). The most common mode of trauma in traumatic CSDH patients was "falls" (61.3%). As for the medical history, the taking of anticoagulants and antiplatelet drugs were more common in NOS CSDH patients than in traumatic CSDH patients (9.0% vs. 1.2%, $P = 0.001$; 13.5% vs. 4.2%, $P = 0.003$). Detailed data was showed in Table 1.

3.3 Traumatic and NOS CSDH patients had similar radiological presentations

As shown in Table 2, there were no significant differences in the CT presentations of hematoma between traumatic and NOS CSDH patients at admission. The most common hematoma location of traumatic and NOS CSDH patients was left side (42.3% vs. 48.1%), followed by right side (35.1% vs. 35.3%), and bilateral (22.6% vs. 16.6%). In traumatic and NOS CSDH patients, the mean value of maximum thickness of hematoma was 18.7 ± 8.2 mm and 20.0 ± 7.5 mm, midline shift of brain was 9.3 ± 4.2 mm and 9.8 ± 4.7 mm, and hematoma volume was 102 ± 64 ml and 109 ± 71 ml. All in all, above data showed that traumatic and NOS CSDH patients had similar CT presentations of hematoma.

3.4 Traumatic and NOS CSDH patients had similar treatment and clinical outcome

As shown in Tables 3, 4, the rate of borehole drainage in traumatic and NOS CSDH patients was similar (78.6% vs. 73.7%, $P = 0.321$). And, the rate of medication therapy including atorvastatin and dexamethasone in two groups was similar as well (62.5% vs. 67.7%, $P = 0.351$; 16.7% vs. 16.5%, $P = 0.977$). The outcome of neurological function at discharge was also similar in traumatic and NOS CSDH patients ($P = 0.909$). Furthermore, the mean hospital stays and total costs of traumatic and NOS CSDH patients were almost equal (9.9 ± 5.4 days vs. 10.1 ± 6.6 days, $P = 0.831$; 2.7 ± 2.4 wan yuan vs. 2.6 ± 2.6 wan yuan, $P = 0.914$). These findings indicated that traumatic and NOS CSDH patients had similar treatment and clinical outcomes.

4 Discussion

This retrospective study explored the clinical differences between traumatic and NOS CSDH patients. Major results were as follows: (1) Compared to NOS CSDH patients, the average age was younger, epilepsy was more frequent, asymptomatic cases were more common, and the application of anticoagulants and antiplatelet drugs were rarer in traumatic CSDH patients. (2) No differences were found in the radiological presentations of hematoma at admission, the treatment methods and clinical outcomes of traumatic and NOS CSDH patients. These findings are meaningful for deeply understanding the clinical characteristics of CSDH.

CSDH is a common neurosurgical disease, with an incidence of 17.2–20.6 per 100,000 persons per year, which is higher in the elderly and likely to reach 17.4 per 100,000 individuals by 2030 due to aging population and increasing use of anticoagulants (9, 16, 17). CSDH is conventionally considered to be a part of traumatic brain injury, which can be induced by isolated head trauma or develop following a traumatic subdural hygroma or mild acute subdural hematoma (18). In our study, traumatic CSDH was defined as patients presented with the main symptoms such as persistent headache, transient disturbance of consciousness or limb weakness that were closely related to head trauma events such as fallen, traffic accidents during the past days or weeks. In the clinical practice, we found a significant proportion of CSDH patients were indeed undergoing head trauma before the development of clinical symptoms of CSDH. Usually, the head trauma is more frequent in younger CSDH patients than in elderly CSDH patients (19). The most common event of trauma in elderly CSDH patients is fallen, but in younger ones is traffic accident (20, 21). The

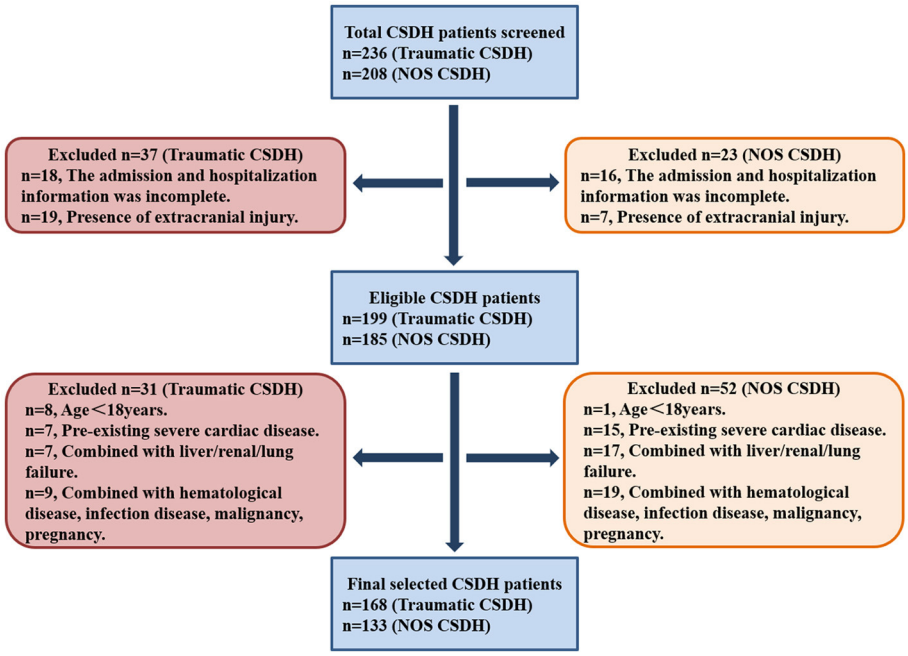

FIGURE 1
The selection flowchart of traumatic and NOS CSDH patients. NOS, not otherwise specified.

higher rate of traumatic CSDH in younger ones might be explained by the fact that most of younger individuals are in a state of working, movement and exercising, resulting in a higher rate of head trauma caused by unintentional injury, traffic accident and fallen. Consistent with these literatures, our study indicated that the mean age of traumatic CSDH patients was younger than NOS CSDH patients, and the most common mode of trauma was "falls." The pathological mechanism in the association of elderly, trauma and CSDH might be an increase in extracerebral volume after age increasing and brain weight declines, which leads to an easily tear of bridging veins and subsequent hematoma formation after trauma. Another cause of the elevated incidence of CSDH in elderly individuals is the increasingly use of anticoagulants and antiplatelet drugs. Many studies reported that a proportion of CSDH patients, especially elderly ones had the prior treatment with anticoagulant and antiplatelet drug (6, 22–24). The rate of CSDH patients treated with anticoagulant drugs was 2.5%−40.6%, and with antiplatelet drugs was 4.5%−44%, which was higher in the elderly and different in different countries (19). We found the rate of taking anticoagulant and antiplatelet drugs in NOS CSDH patients was 9.0% and 13.5% respectively, which was obviously higher than in traumatic CSDH patients. Taking together, these results indicated that NOS CSDH patients were more common in the elderly, and had a higher rate of taking anticoagulant/antiplatelet drugs, compared to traumatic CSDH patients.

CSDH patients often begin to manifest symptoms after the intracranial volume is overwhelmed by the expanding hematoma, which is usually diverse and includes headache, gait disturbance, hemiparesis, and cognitive problems (25, 26). One latest study indicated that the most prevalent symptoms in CSDH patients were focal neurological deficit (46%), headache (41%), gait disorder (31%), and cognitive complaint (31%) (27). Similarly, our study found that headache and limb weakness were the most common symptoms in both traumatic and NOS CSDH patients. Moreover, our results indicated that epilepsy was more frequent and asymptomatic cases were more common in traumatic CSDH patients, compared to NOS CSDH patients. This result might be explained by the fact that traumatic CSDH is one of the major predictor of seizure (28). Traumatic CSDH is one type of traumatic brain injury, which is a well-established risk factor for seizure (29). The severity of brain trauma was not only a predictor for early seizure, but also a major predictor for late seizures and post-traumatic epilepsy (28). Accordingly, epilepsy was more frequent in traumatic CSDH patients might be explained the fact that those patients were often combined with a mild or moderate brain trauma, a potential inducement of late seizures and post-traumatic epilepsy. Seizure is a rare and prominent sign, which reflects the extreme clinical manifestation of CSDH. Some studies demonstrated that CSDH patients with seizure would have a worse outcome (28), but another study did not find an association between the seizure and poor outcome of CSDH (27). Moreover, seizures after CSDH surgery, mainly refer to burr hole craniotomy, were associated with postoperative complications, higher mortality and poorer clinical outcomes at follow-up (30). And, larger post-operative depressed brain volume was the only factor independently associated with suspected postoperative seizure, and it could help identify a subgroup of CSDH patients with higher susceptibility to epileptic events (31). Although seizure is an offensive complication after surgery in CSDH patients, no studies have demonstrated the postoperative use of antiepileptic drugs can lead to better clinical outcomes.

TABLE 1 Baseline characteristics of traumatic/NOS CSDH patients at admission.

Variable	Traumatic CSDH	NOS CSDH	T/χ^2	*P*-value
Gender (*n*, %)			4.639	0.031
Male	147 (87.5%)	104 (78.2%)		
Female	21 (12.5%)	29 (21.8%)		
Age (y)	65.9 ± 16.3	70.8 ± 13.0	−2.803	**0.005***
Main symptoms (*n*, %)			23.613	**<0.001***
Headache & dizziness	74 (44.1%)	77 (57.9%)		
Limb weakness	55 (32.7%)	43 (32.3%)		
Epilepsy	13 (7.7%)	4 (3.0%)		
No symptoms	26 (15.5%)	9 (6.8%)		
Initial GCS	14.1 ± 1.7	14.2 ± 1.9	−0.346	0.715
Mode of trauma			/	/
Traffic accidents	65 (38.7%)	/		
Falls	103 (61.3%)	/		
Medical History (*n*, %)				
Hypertension	57 (33.9%)	51 (38.3%)	0.630	0.428
Coronary heart disease	11 (6.5%)	6 (4.5%)	0.578	0.447
Diabetes	25 (14.9%)	13 (9.8%)	1.755	0.185
Anticoagulant drug	2 (1.2%)	12 (9.0%)	10.268	**0.001***
Antiplatelet drug	7 (4.2%)	18 (13.5%)	8.553	**0.003***
Smoking history	87 (51.8%)	54 (40.6%)	3.729	0.053
Drinking history	88 (52.4%)	62 (46.6%)	0.987	0.321

CSDH, chronic subdural hematoma; NOS, not otherwise specified; GCS, Glasgow Coma Scale. $P < 0.05$ represents statistically significant (marked with * and bold).

TABLE 2 Radiological parameters of traumatic/NOS CSDH patients at admission.

Variable	Traumatic CSDH	NOS CSDH	T/χ^2	*P*-value
Hematoma location (*n*, %)			1.945	0.378
Left side	71 (42.3%)	64 (48.1%)		
Right side	59 (35.1%)	47 (35.3%)		
Bilateral	38 (22.6%)	22 (16.6%)		
Maximum thickness (mm)	18.7 ± 8.2	20.0 ± 7.5	−0.881	0.381
Midline shift (mm)	9.3 ± 4.2	9.8 ± 4.7	−0.636	0.514
Hematoma volume (ml)	102 ± 64	109 ± 71	−0.742	0.453

CSDH, chronic subdural hematoma; NOS, not otherwise specified.

TABLE 3 Treatment of traumatic and NOS CSDH patients.

Variable	Traumatic CSDH	NOS CSDH	T/χ^2	*P*
Borehole drainage (*n*, %)			0.984	0.321
With	132 (78.6%)	98 (73.7%)		
Without	36 (21.4%)	35 (26.3%)		
Atorvastatin (*n*, %)			0.869	0.351
With	105 (62.5%)	90 (67.7%)		
Without	63 (37.5%)	43 (32.3%)		
Dexamethasone (*n*, %)			0.001	0.977
With	28 (16.7%)	22 (16.5%)		
Without	140 (83.3%)	111 (83.5%)		

CSDH, chronic subdural hematoma; NOS, not otherwise specified.

Non-contrasted head CT is the mainstay and initial diagnostic method for CSDH, which can reflect the radiological outcomes of hematoma included hematoma location, maximum thickness, midline shift and hematoma volume. Our study showed that traumatic and NOS CSDH patients had similar CT presentations of hematoma, and the most common hematoma was left side, followed by right side and bilateral. According to the hematoma density on CT scan, CSDH is categorized into five subtypes including high, moderate, low, mixed, and layering (32). According to the internal architecture of the hematoma on CT scan, CSDH is categorized into four subtypes including homogeneous, laminar, separated, and trabecular, which is considered to reflect the four stages of the natural progression of the disease (33). Head CT at the time of trauma preceding CSDH usually showed thin subdural effusion, which was often close to the detection limit of CT immediately, but became more apparent from the day after the injury (34). Moreover, some researchers found no benefit for routine follow-up CT after surgery for CSDH over CT performed only in patients with clinical deterioration or persisting neurologic deficits (35). Based on these literatures, conducting in-depth research on the preoperative CT classification and postoperative follow-up CT is essential for the diagnosis of CSDH and the prediction of recurrence after surgery.

The treatment strategy of CSDH patients consists of surgical evacuation of the hematoma, the medication therapy including dexamethasone and atorvastatin, and conservative observation. Surgical intervention is recommended for CSDH patients who manifest as neurologic symptoms with associated clinical or radiographic evidences of cerebral compression (36). The main surgical treatment in symptomatic patients including twist drill craniotomy (TDC), burr-hole craniotomy (BHC) and craniotomy, which can evacuate the hematoma effectively and is often combined with the placement of a subdural or sub-periosteal drain (15, 37, 38). Generally, the outcomes after surgery of symptomatic CSDH are favorable, with rapid clinical improvement occurring in over 80% of patients (39). However, the overall surgical mortality ranges widely from approximately 0% to 32%, and the operative morbidity ranges from approximately 3% to 12% (36, 40, 41). TDC is the most minimally invasive surgery for CSDH, which creates a small (<5 mm) burr hole and is usually performed at bedside through local anesthesia (25). The advantages of TDC include

the minimum invasiveness, the avoidance of general anesthesia and the lower overall procedural risk, particularly in patients older than 60 years or have medical comorbidities (42, 43). The morbidity and mortality associated with TDC was 2.5%−4.4% and 2.9%−5.1% respectively (40, 44), significantly lower than other surgical methods. However, the hematoma evacuation rate of TDC was obviously lower than other surgical techniques, resulting in a higher recurrence rate of CSDH ranging from 28.1%−31.3% (40, 44). BHC is the most common surgery for CSDH, which is performed by drilling one or two 12–14 mm burr holes on the cerebral convexity 5–8 cm apart firstly, and evacuating the hematoma by suction and irrigation subsequently (15, 45). Normal saline is the most commonly used irrigation solution, artificial cerebrospinal fluid and the solution at body temperature are two new-type irrigation solutions, which were reported to reduce the recurrence rate of CSDH (46, 47). BHC is most commonly performed under general anesthesia, though local anesthesia is a feasible alternative one with lower complication rates (48, 49). The morbidity and mortality of BHC was 4%−9.3% and 2.5%−3.7% respectively, and the recurrence rate of CSDH after BHC was 10.5%−12.0%, obviously lower than the recurrence rate after TDC (39, 40, 50). Craniotomy is the most invasive and surgically effective, but less frequently performed surgery for CSDH, which creates a skull bone window at 3–5 cm in diameter and incises the dura to evacuate the hematoma and allow fluid to drain out of the subdural space (51). The advantages of craniotomy include this technique can evacuate the hematoma thoroughly, excise the hematoma membrane and coagulate the bleeding point precisely under a direct vision (52). The morbidity and mortality correlated with craniotomy was 4%−12% and 4.6%−12.2% respectively, significantly higher than TDC and BHC (39, 40, 44, 50), the recurrence rate after craniotomy was 11%−19.4%, higher than BHC and lower than TDC (40, 41). Other newly developed surgical techniques including the "Hollow screw system" is applied as a less invasive surgery for elderly patients with CSDH (53), the endoscope is used for recurrent or complicated hematoma cases, and middle meningeal artery (MMA) embolization is considered a promising treatment for patients with initial and/or recurrent CSDH (54). Hollow screw system is a modification of TDC, in which a hollow screw is threaded through a twist-drill hole and is connected to a closed drainage system, without the insertion of a catheter into subdural space (53). One latest meta-analysis indicated that TDC with hollow screws was not inferior or superior to BHC in efficacy, but was safer and minimally invasive, which reflected in a lower incidence of acute brain hemorrhage, overall complication and longer hospital stays (55). Neuroendoscopy can be used in both BHC and craniotomy, which provides enhanced visualization of the hematoma, the trabeculae, and septation (56, 57). The visualization of neuroendoscopy can further facilitate more complete hematoma evacuation, more precise hematoma membrane excision and meticulous microscopic hemostasis, resulting in low complication rates and reduced recurrence rates (22, 58). MMA embolization can inhibit hematoma expansion and recurrence by embolizing the subdural neomembrane capillaries through the catheter-based endovascular intervention technique (59, 60). Several single-cohort and multi-center studies have demonstrated that MMA embolization in conjunction with surgical evacuation can effectively reduce recurrence rates and is associated with low procedural complication rates (61–65). The conservative observational approach and medical treatment is appropriate for asymptomatic CSDH patients who have mild symptoms such as headache only, but have no sign of cerebral compression. Glucocorticoid therapy, mainly refers to dexamethasone, has been proposed as an alternative, non-operative treatment for CSDH, which has the potential to block inflammation in subdural space, thereby impeding hematoma persistence and growth (66). Although glucocorticoids were reported to be safe and effective as a therapy for CSDH, two recent randomized controlled trials have demonstrated that dexamethasone resulted in fewer favorable outcomes and more adverse events than placebo (66, 67). Another effective medical treatment is atorvastatin, which could lead to a reduction in CSDH volume without the requirement for surgery and showed no adverse effects (68–72). One double-blind, randomized, placebo-controlled phase II clinical trial found the atorvastatin at 20 mg daily to be safe, effective and cost effective for non-surgically treating patients (68). Another open-label, evaluator-blinded trial found that compared with atorvastatin alone, the combination of atorvastatin and low-dose dexamethasone accelerated hematoma reduction and neurological improvement in CSDH patients (69). Moreover, atorvastatin administration after surgery was reported to reduce hematoma volume and improve neurological function, but barely reduced the recurrence rate of hematoma (70). On the contrary, one latest study demonstrated that an administration of atorvastatin of 20 mg daily for 4 weeks may be helpful in reducing the recurrence rate of CSDH following BHC surgery without any serious adverse effects (71). Our research found the rate of BHC in traumatic and NOS CSDH patients was 78.6% vs. 73.7%, and, the rate of atorvastatin therapy was 62.5% vs. 67.7%, dexamethasone therapy was 16.7% vs. 16.5%. At last, most of the traumatic and NOS CSDH patients acquired neurological function improvement at discharge.

Based on the above research findings, several potential implications for clinical practice might be worth mentioning. Firstly, detailed medical history of head trauma and taking of anticoagulants/antiplatelet drugs should be inquired carefully in younger and older CSDH patients respectively. Secondly, more attention should be paid to the prevention, diagnosis and treatment of epilepsy in younger CSDH patients in the perioperative period,

TABLE 4 Clinical outcome of traumatic and NOS CSDH patients at discharge.

Variable	Traumatic CSDH	NOS CSDH	T/χ^2	*P*
Neurological function (*n*, %)			0.19	0.909
Improvement	103 (61.3%)	84 (63.2%)		
No change	48 (28.6%)	35 (26.3%)		
Deterioration	17 (10.1%)	14 (10.5%)		
Hospital stays (days)	9.9 ± 5.4	10.1 ± 6.6	−0.213	0.831
Total costs (wan yuan)	2.7 ± 2.4	2.6 ± 2.6	0.109	0.914

CSDH, chronic subdural hematoma; NOS, not otherwise specified.

especially the ones with medical history of head trauma. Thirdly, the selection of treatment protocols for traumatic and NOS CSDH patients should be mainly made according to the outcome of CT/MRI scan.

There are some objective limitations in this study should be considered. First, this study is an observational and retrospective one without active intervention and long-term follow-up visits. Second, the number of patients is relatively small and the ill condition of recruited patients is mainly mild to moderate as the mean GCS in two groups was about 14. Finally, BHC was the only surgical treatment for CSDH patients in this study, making the comparison of curative effects between different surgical methods to be impossible. Therefore, it is very necessary to conduct prospective, large sample and in-depth clinical study to explore this issue in the future.

In conclusion, this retrospective study explored the clinical differences between traumatic and NOS CSDH patients. Compared to NOS CSDH patients, the average age was younger, epilepsy was more frequent, asymptomatic cases were more common, and the taking of anticoagulants and antiplatelet drugs were rarer in traumatic CSDH patients. However, no differences were found in the radiological presentations of hematoma at admission, the treatment methods and clinical outcomes of traumatic and NOS CSDH patients. These findings are meaningful for deeply understanding the clinical characteristics of CSDH.

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 study involving humans was approved by the Ethics Committee of the faculty of The General Hospital of Western Theater Command. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YY: Writing – original draft, Writing – review & editing. XZ: Data curation, Formal analysis, Investigation, Writing – original draft. TY: Data curation, Investigation, Methodology, Writing – review & editing. KF: Data curation, Investigation, Writing – review & editing. JC: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. YM: Data curation, Investigation, Methodology, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The present work was supported by grants from the National Natural Science Foundation of China (82101465 to Yongxiang Yang) and the Natural Science Foundation of Sichuan Province (2022NSFSC1444 to Yongxiang Yang).

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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frontiers | Frontiers in Surgery

TYPE Case Report
PUBLISHED 08 November 2024
DOI 10.3389/fsurg.2024.1455178

OPEN ACCESS

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RECEIVED 26 June 2024
ACCEPTED 09 October 2024
PUBLISHED 08 November 2024

CITATION
Xue H, Li W, Zhang W, Sun L, Li Y and Yang H (2024) Transoral penetrating craniocerebral injury: a case report and literature review. Front. Surg. 11:1455178.
doi: 10.3389/fsurg.2024.1455178

Transoral penetrating craniocerebral injury: a case report and literature review

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A penetrating brain injury is a rare type of neurosurgical trauma associated with extremely high mortality and disability rates. Penetrating skull base injuries caused by arrows seldom occur because injuries caused by such weapons are more likely to be accidental. However, the number of self-inflicted injuries is increasing, and these injuries have varying patterns and high mortality rates. We report a case of a transoral penetrating craniocerebral injury caused by an arrow in a suicidal patient. Preoperative imaging is crucial for detecting and planning the surgical approach. Surgery is an effective treatment for this type of injury. Additionally, we reviewed previous case reports on this type of injury to provide recommendations for its clinical detection and treatment.

KEYWORDS
arrow, suicide, transoral, penetrating craniocerebral injury, surgery

Introduction

Transoral penetrating craniocerebral injuries are a rare complication of neurosurgery, and their primary treatment is craniotomy due to the presence of a foreign body. Craniocerebral CT is the main imaging method for this condition, and cranial reconstruction is an important basis for formulating relevant surgical protocols. Because the incidence of postoperative intracranial infection is extremely high, antibiotics are necessary to prevent and treat infection.

Case description

A 20-year-old male patient was admitted to the Neurotrauma Surgery Department of Jilin University First Hospital due to attempted suicide by shooting an arrow through his mandible into his skull approximately 7 h prior. He had a 2-year history of depression, which was moderately controlled with regular oral medication. On physical examination upon admission, the patient was conscious, with a GCS score of E3VTM6. The arrow penetrated the skin and was visible in the mandibular region, and the tail of the arrow was outside the body (Figure 1A). The diameter of both pupils was 3.0 mm, and his reflexes to direct and indirect light were slow; his limb muscle strength was grade 5, his muscular tone was normal, and he had negative bilateral Babinski signs. Preoperative craniocerebral CT revealed tubular high-density shadows in the brain tissue, with the upper margin reaching the frontal bone and the lower margin extending to the right

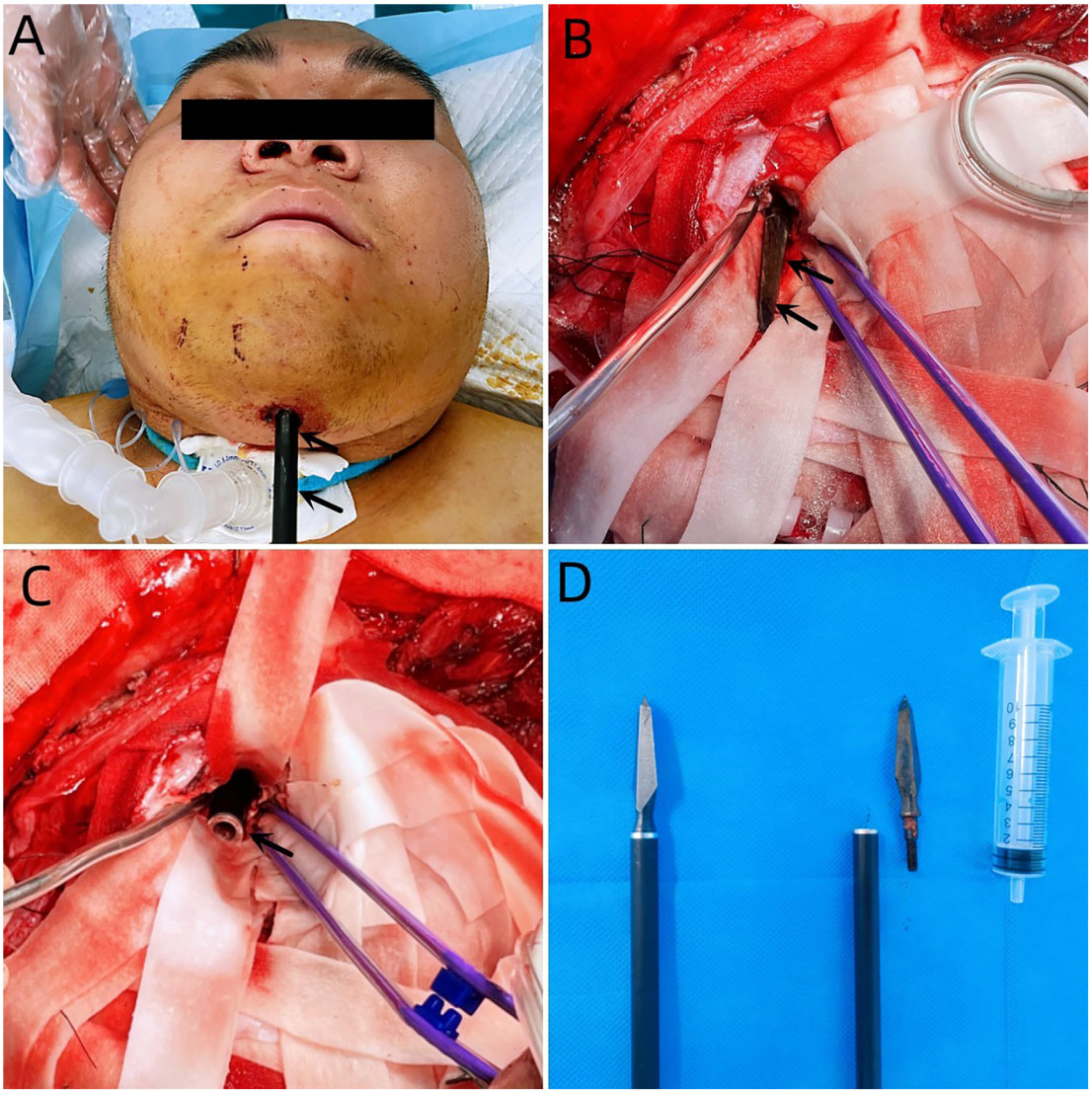

FIGURE 1
(A) Penetration of the skin of the mandibular region with an arrow, with its tail outside the body. (B) The black arrow indicates the head of the arrow. (C) The black arrow indicates the tail of the arrow. (D) The right image shows the intraoperative removal of the arrow, and the left image shows the arrow.

nasal region through the skull base (Figures 2, 3). Maxillofacial CT and 3D reconstruction revealed that a thin tubular foreign body had penetrated the submentum, tongue, oral cavity, right nasal cavity and ethmoid sinus, extending intracranially (Figure 4). During surgery, craniotomy was performed with a milling cutter at the transverse midline of the frontotemporal flap on the affected side. After the dura mater was exposed, local damage to the dura mater was observed, with the arrow exposed and dark red venous blood overflowing along the edge of the arrow. Bleeding was completely stopped by rinsing with hydrogen peroxide and gentamicin, after which the dura mater was cut radially. The dura mater was incised, and the subarachnoid space was opened to release cerebrospinal fluid and therefore allow slow decompression. After the collapse of the brain tissue comprising the frontal lobe, the hematoma and brain tissue damaged by the arrow were removed, the section of the arrow that extended intracranially was gradually exposed, the arrow was fixed with a bone rongeur, and the external shaft of the arrow was gently rotated until the head of the arrow was completely separated (Figure 1B) from the shaft of the arrow (Figure 1C). The head of the arrow was removed, and the shaft of the arrow was extracorpotruly retracted until it was completely removed from the skull (Figure 1D). After the damaged area of the skull base was fully exposed and the surrounding brain tissue was protected, the temporal fascia and artificial dura mater were removed to repair the damaged area of the skull base. After the skull base was completely repaired, active bleeding in the1 surgical area was 1absent, and the bone flap was also reset. The otolaryngologist subsequently continued to perform surgery to treat the nasopharyngeal injury. Postoperative craniocerebral CT reexamination revealed that the intracranial foreign body was completely removed, without residue or secondary intracranial

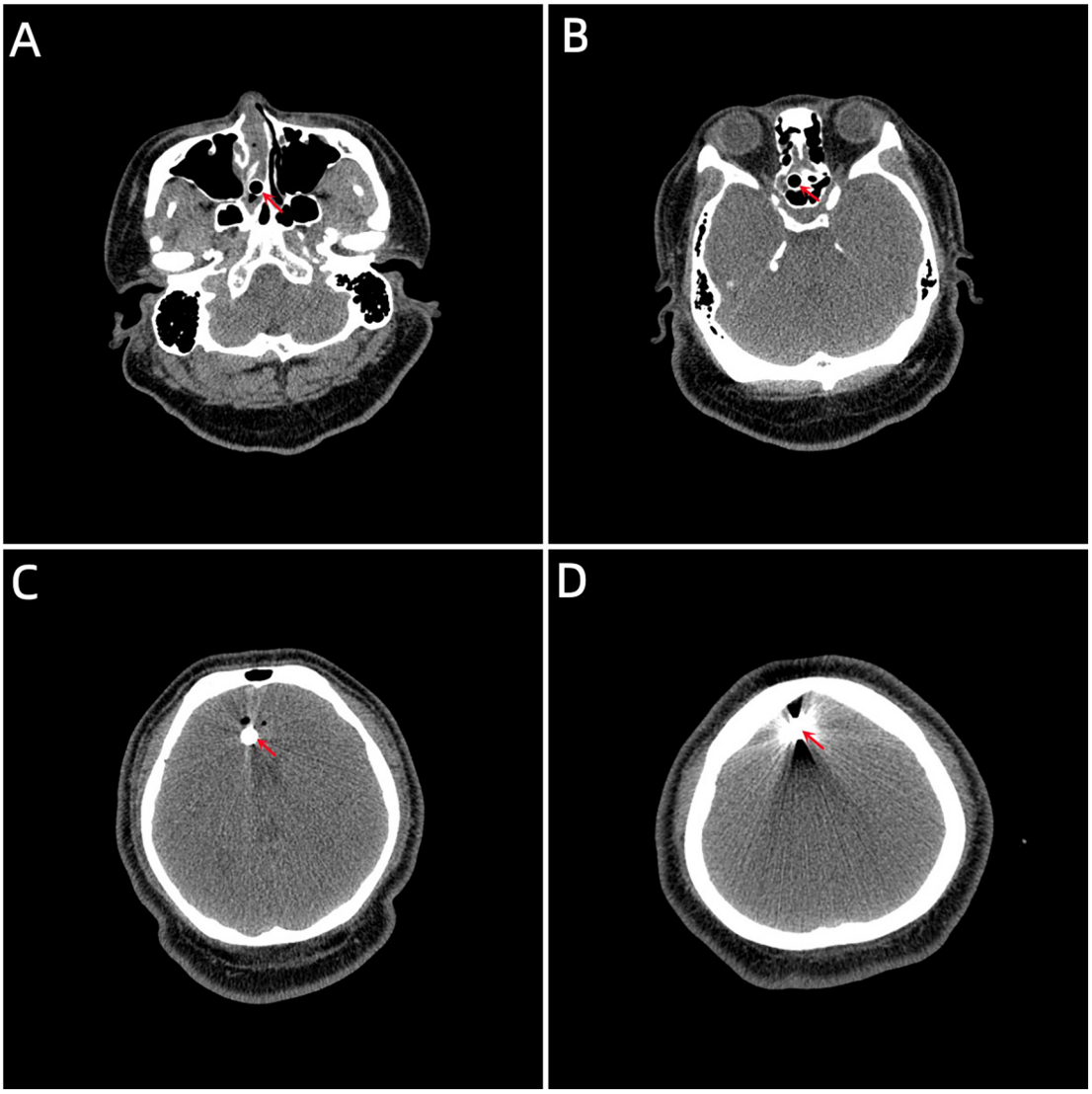

FIGURE 2
(A) The lower margin extending to the right nasal region through the skull base. (B, C) Tubular high-density shadow in the brain tissue. (D) The upper margin reaching the frontal bone. (the red arrow indicates the location of the foreign body location).

hemorrhage (Figure 5). After surgery, the patient was administered cefminol sodium to prevent intracranial infection. He recovered well and did not exhibit signs of neurological sequelae at the 6-month follow-up visit.

Discussion

Penetrating brain injuries are serious and have high mortality and morbidity rates (1). Arrow-induced intracranial injury is rare, and injuries caused by such weapons have historically often been accidental. However, the number of self-inflicted injuries has increased; these injuries have varying patterns and a relatively high mortality rate (1–3). PBIs caused by objects with impact velocities <100 m/s, such as metal, wood, and plastic objects, are referred to as nonfirearm penetrating brain injuries. The mechanism of craniocerebral dynamic injury is direct tearing of the injury tract (4).

Although penetrating brain injories are rarer than closed brain injuries, their prognosis is usually poor (5). These injuries mostly occur in males aged 6–55 years, with the most common cause being accidents during exercise and the second most common cause being suicide attempts (1–3, 6–8). These two causes often vary in entry location and trajectory. In accidental injuries, the arrow usually enters the skull from the frontal or occipital region. A transoral penetrating injury is a common injury associated with violent suicide (2). This type of injury is caused by gunfire (9, 10), whereas craniocerebral injury is caused by means other than gunfire (e.g., low-velocity penetrating craniocerebral injury) and is extremely rare (3). According to previous reports, 75% (12/16) of such injuries are related to suicide (Table 1). In suicide attempts, arrows usually

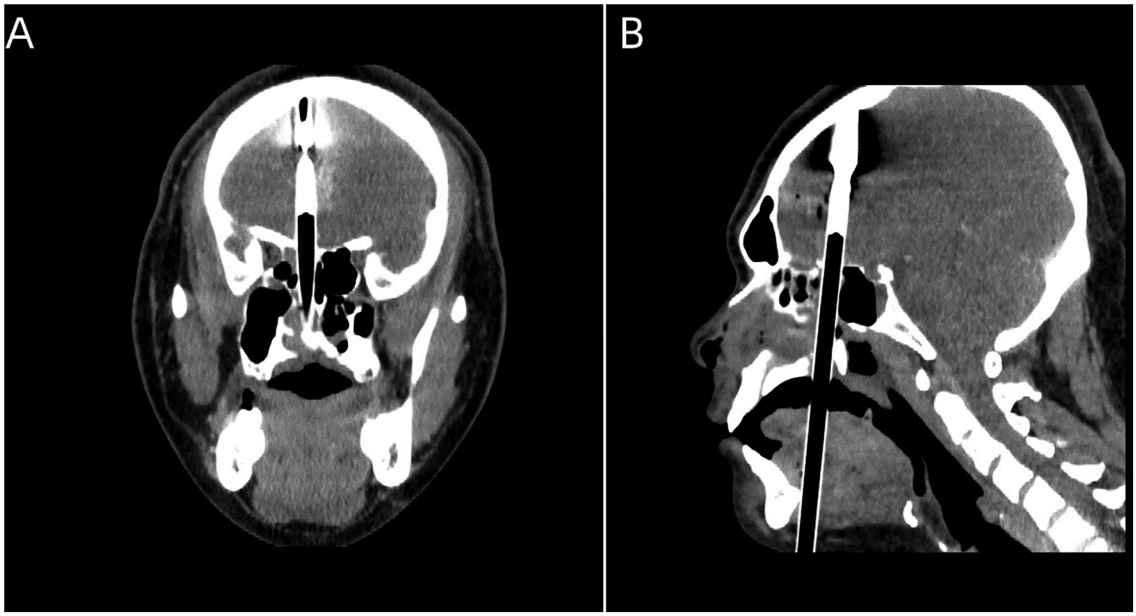

FIGURE 3
(A) Coronal view of the foreign body. (B) Sagittal view of the foreign body.

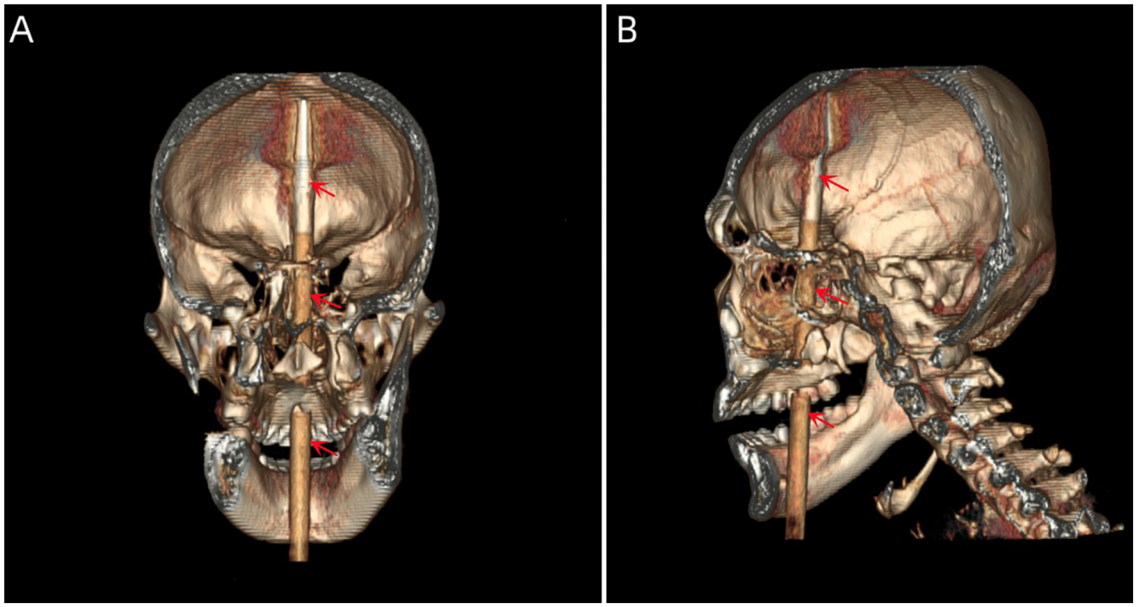

FIGURE 4
(A, B) 3D reconstructed images showing the location of the foreign body within the skull (the red arrow indicates the foreign body).

enter through the submental or submandibular region of the mouth (1). The trajectory of the arrow is directly associated with the location of the brain injury—an injury to a major artery or the venous sinus is associated with an increased risk of vascular complications (1).

Imaging examination is essential for determining the shape, size and trajectory of the penetrating foreign body, as well as to correctly diagnose the injury and select the appropriate surgical protocol (16–21). The missed detection rate of CT for nonmetallic foreign bodies is 42% (10). Several cases missed

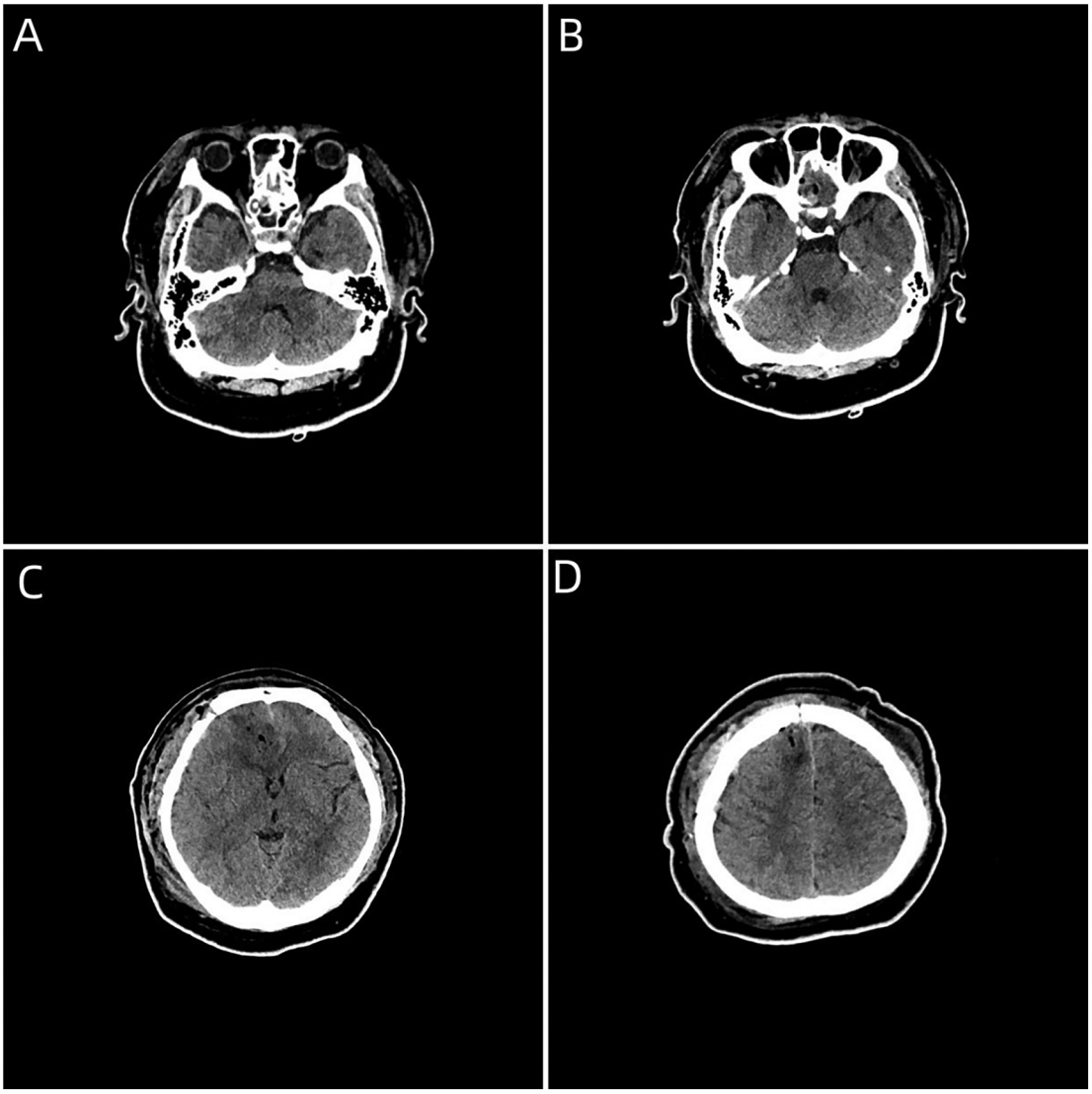

FIGURE 5
(A–D) Postoperative craniocerebral CT image showing complete removal of the intracranial foreign body, without foreign body residue or secondary bleeding complications.

detections on CT images have been reported (16, 22, 23). The density of woody foreign bodies increases over time, possibly due to granulomas around the foreign bodies or calcium deposits inside the wood (16). Therefore, the density of foreign bodies is similar to that of brain tissue, which hinders their identification on CT. Accordingly, metallic foreign bodies are more easily diagnosed with CT, whereas MRI has great value for the identification of woody foreign bodies. Specifically, MRI helps distinguish the woody foreign body from the surrounding air and fat tissue (24). Notably, MRI may cause the movement of metal foreign bodies and may require a longer examination time. Because our patient's intracranial foreign body was made of metal (arrowhead), the patient was unable to undergo a brain MRI examination. Cerebral angiography is recommended for diagnosing transoral penetrating craniocerebral injury after ruling out cerebrovascular injury, and the association between the foreign body and the intracranial vasculature can be examined (16). Unfortunately, cerebral angiography was not performed because the equipment in our hospital was damaged on that day. CT angiography should be performed to investigate the cerebrovascular injuries either by the location or trajectory of the foreign body after an intracranial penetrating trauma. CT angiography is accurate in detecting most traumatic intracranial aneurysms, dissections, and occlusions or for revealing the location of hematomas.

Currently, clinical data are insufficient to provide an appropriate antibiotic regimen for penetrating brain injuries. Intracranial infections following penetrating brain injuries are generally associated with an increased risk of mortality (5). The rates of local wound infection, meningitis and brain abscess are elevated among patients with PBI secondary to contamination from foreign objects and skin and bone fragments introduced

TABLE 1 Reported cases of transoral penetrating craniocerebral injury.

Reference	Age (years)	Gender	Cause	Material	Interval to operation	Antibiotics used	Infection	Outcome
Ban LH et al., (8)	43	Male	Suicide	Speargun	Not clear	Amoxicillin/Cla-vulanate	No	Left facial palsy, Cerebellar signs
Hettige S et al., (13)	38	Woman	Accident	Chopsticks	Not clear	Not clear	Not clear	Auditory and visual deterioration
Abarca-Olivas J et al., (6)	34	Male	Suicide	Speargun	2 h	Not clear	No	No neurological deficit
Sweeney JM et al., (14)	31	Male	Suicide	Knife	Not clear	Not clear	Not clear	Not clear
Khayat MA et al., (15)	31	Male	Suicide	Crossbow arrow	Not clear	Not clear	Not clear	Not clear
Aljuboori Z et al., (32)	36	Male	Suicide	Arrow	Not clear	Not clear	Not clear	No neurological deficit
	22	Male	Suicide	Arrow	Not clear	Not clear	Not clear	No neurological deficit
	67	Male	Suicide	Arrow	Not clear	Not clear	Not clear	CSF leak
Joly LM et al., (33)	42	Male	Suicide	Arrow	Not clear	Not clear	meningitis	No neurological deficit
Williams JR et al., (3)	55	Male	Suicide	Fishing harpoon gun	4.5 h	Ceftriaxone, vancomycin, metronidazole, meropenem, vancomycin	Brain abscess	Died
Bakhos D et al., (7)	35	Male	Suicide	Speargun	Not clear	Ceftriaxone, Ornidazole, amoxicillin	No	No neurological deficit
Lan ZG et al., (4)	25	Male	Accident	Metal rod	Not clear	Ceftriaxone, metronidazole	No	Not clear
Barranco R et al., (2)	59	Male	Suicide	Speargun	Not clear	Not clear	Not clear	Died
Yoneoka Y et al., (12)	65	Male	Accident	Garden pole	7 days	Piperacillin	No	No neurological deficit
Oearsakul T et al., (1)	26	Male	Suicide	Speargun	Not clear	Not clear	Not clear	No neurological deficit
Widodo D et al., (28)	28	Male	Accident	Wood	2 days	Not clear	No	No neurological deficit

into the brain parenchyma along the projectile track. Before the advent of antibiotics, the rate of these infectious complications was reported to be as high as 58.8% in the military population (5). According to our review of previous cases, all but 12 patients, whose data were not explicitly recorded, were treated with antibiotics (Table 1). The infection rate was 28.6% (2/7) (9 patients did not explicitly claim to be infected) (Table 1).

Broad-spectrum antibiotics are most commonly used for treatment (16, 25). The method to select the most suitable prophylactic antibiotic regimen for patients with penetrating brain injuries varies. Cephalosporins are the most commonly used antibiotics (26). Esposito and Walker recommended treating penetrating brain injury patients with intravenous ceftriaxone, vancomycin and metronidazole for at least 6 weeks (27). Previous studies clearly indicate that all prophylactic antibiotics are broad-spectrum antibiotics (Table 1). Notably, the overuse of antibiotics can increase the risk of fungal infections. Widodo D therefore recommended the commencement of this therapeutic regimen as soon as possible after craniocerebral injury and its continuation for 5 days postoperatively (27). However, given the rarity of this condition, relevant reports are scarce; therefore, the various antibiotic treatment regimens still need further research.

The application of antiepileptic drugs has also been studied in this context. Today, the use of anticonvulsant drugs within the first 7 days of this injury is believed to be beneficial (3). However, the preventive use of anticonvulsant drugs for periods longer than 7 days is controversial. Nevertheless, the latest evidence shows that given the high incidence of epilepsy during the course of the disease, the benefits of continued use of anticonvulsant drugs are greater than their adverse effects (3).

The goal of surgical treatment for a transoral penetrating craniocerebral injury is to reduce the space-occupying effect of the foreign body and reduce the risk of infectious complications (5). Surgery is the major strategy for treating transoral penetrating craniocerebral injury (3, 26, 28, 29). Surgical indications for this injury include fracture displacement, cerebrospinal fluid leakage, foreign body residue, vascular injury and intracranial hemorrhage (3, 28, 29). However, the amount of foreign body residue or intracranial hemorrhage indicated for surgery have not been reported. Some small foreign bodies or those adjacent to important exposed structures, such as the brainstem, can be treated conservatively, and surgery should be performed within 12 h of injury (28). However, active debridement of deep fragments should be avoided because this procedure increases the risks of disability and mortality (3, 28, 29).

Early complications include vascular injury, ischemic injury, cerebral contusion hemorrhage, cerebral edema and infection, whereas late complications include hydrocephalus, cerebrospinal fluid leakage and infection (30). Early infections are associated with debris (foreign bodies, bone fragments, and hair or skin penetrating the brain) (30). Infections, including extracranial and intracranial infections such as wound infection, cranial

osteomyelitis, meningitis and brain abscess, account for 5%–23% of complications. These infections are often linked to cerebrospinal fluid leakage, debris impingement and sinus wounds (30, 31). Cerebrospinal fluid leakage usually occurs as a result of dura mater tears that fail to heal. They most commonly occur at the entry wound site (or at the exit in cases of bullet injury), are present in up to 9% of patients and are highly predictive of intracranial infections (11, 30). Intranasal topical application of fluorescein is conducive to detecting cerebrospinal fluid leakage, and autologous transplantation of epifascial adipose tissue can be performed to repair cerebrospinal fluid leakage. The use of a fat-on-fascia plug shortens the surgical time, thereby reducing the risk of aerosolization during surgery (12). Specifically, minimal intranasal submucosal dissection reduces the operative time and the risk of virus "aerosolization". In addition, the described fat-on-fascia plug method does not require the placement of a mucosal pedicle flap, which also reduces the operative time and the risk of virus aerosolization.

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 studies involving humans were approved by The First Hospital of Jilin University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HX: Formal Analysis, Writing – original draft, Writing – review & editing. WL: Writing – review & editing. WZ: Writing – review & editing. LS: Writing – review & editing. YL: Writing – review & editing. HY: Funding acquisition, Resources, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 21 January 2025
DOI 10.3389/fneur.2024.1444623

OPEN ACCESS

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RECEIVED 05 June 2024
ACCEPTED 31 December 2024
PUBLISHED 21 January 2025

CITATION
Félix J, Araújo L, Henriques A, Pereira A and Carneiro S (2025) Use of amantadine in traumatic brain injury: an updated meta-analysis of randomized controlled trials. *Front. Neurol.* 15:1444623.
doi: 10.3389/fneur.2024.1444623

Use of amantadine in traumatic brain injury: an updated meta-analysis of randomized controlled trials

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Introduction: Amantadine has been shown to accelerate cognitive and functional brain recovery after cerebrovascular accidents. However, the efficacy of this drug in TBI patients remains poorly defined.

Methods: We performed a systematic review and meta-analysis of randomized trials (RCTs) evaluating the effects of amantadine in TBI patients. The Cochrane, Embase, and PubMed databases were systematically searched for trials published up to March 24, 2024. Data from previous RCTs were extracted and quality assessed according to Cochrane recommendations. Means and standard deviations with 95% confidence intervals were aggregated across studies. The primary outcomes assessed were Glasgow Coma Scale (GCS), Mini Mental State Examination (MMSE) and the Disability Rating Scale (DRS).

Results: From 1,292 database results, 6 studies with 426 patients were included, of which 205 received amantadine (48.12%). The Glasgow Coma Scale score on day 7 (MD 1.50; 95% CI 0.08–2.92; $p = 0.038$; $I^2 = 68\%$) was significantly higher in patients treated with amantadine than those treated with placebo. The Mini Mental State Examination (MD 3.23; 95% CI 0.53–5.94; $p = 0.019$; $I^2 = 0\%$) was also better in patients treated with amantadine. No significant differences in Disability Rating Scale, day 3 GCS, Glasgow Outcome Scale (GOS), length of hospital stay, or duration of mechanical ventilation were observed between amantadine and placebo groups.

Conclusion: In our analysis, TBI patients benefit from the use of amantadine in the day 7 GCS score and show better results in the MMSE test, but placebo patients benefit from not using amantadine in the DRS between weeks 3 and 4. No other statistically significant results were found related to the use of this medication.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024538110, CRD42024538110.

KEYWORDS

amantadine, traumatic brain injury, neurotrauma, meta-analysis, placebo

1 Introduction

Traumatic Brain Injury (TBI) is an important cause of death and disability worldwide (1). The global annual incidence of TBI was estimated at 27 million (2). The condition progresses to loss of consciousness and often leads to permanent neurocognitive sequelae for the patient due to the different forms of possible neurological injury, such as extrinsic compression from mass lesion, contusion, diffuse axonal injury [DAI] (3).

There are several general measures for the management of patients with TBI, including euvolemia, 30° head position, use of prophylactic anticonvulsants, and correction of hypoxemia, hypoventilation, and hypotension (4). In addition to these measures, several medications have been used to directly improve the level of consciousness in TBI patients, such as corticosteroids, progesterone, and erythropoietin (5–8). One of these drugs, amantadine, is a neurostimulant commonly used to treat Parkinson's disease. Drugs with dopaminergic effects provide wakefulness and improve nervous system damage by stimulating the reticular activating system (9, 10). The drug is also an antagonist of the N-methyl-D-aspartate receptor (NMDARs) and has anti-inflammatory effects on the brain (11). The drug has been reported to contribute to neurocognitive improvements in patients with TBI, both its direct agonistic effect on dopamine receptors and its NMDARs antagonist effect (10–12).

Two studies (13, 14) found favorable results for amantadine in the first 4 weeks of treatment when the drug was used for less than 1 month, whereas one randomized controlled trial (10) found no benefit with the use of amantadine compared to placebo regardless of the time of administration. In contrast, Giacino and Meythaler (12, 13) found an improvement in Disability Rating Scale (DRS) when patients are treated with amantadine versus placebo. Therefore, there is still disagreement in the literature regarding the use of amantadine in TBI. Although none of the previous meta-analyses analyzed patients' cognitive improvement by each functional outcome scale. Similarly, there are still no analyses comparing mean length of hospital stay (LHS) or mean time on mechanical ventilation (MTMV) in patients treated with amantadine or placebo. In this sense, our analysis will add value by the precision of the scales used in the analysis and by being the first study to evaluate hospitalization measures.

We aim to perform a meta-analysis of randomized controlled trials (RCTs) comparing amantadine and placebo on functional improvement in patients with TBI.

2 Materials and methods

2.1 Eligibility criteria

The inclusion criteria of this meta-analysis was restricted to studies that met all the following eligibility criteria: (1) enrolling patients with traumatic brain injury; (2) comparing amantadine versus placebo; and (3) reporting of at least one outcome of interest. We excluded studies with (1) no control group; (2) no outcomes of interest; (3) non-randomized; and (4) patients without TBI.

2.2 Search strategy and data extraction

This systematic review and meta-analysis adhered to the recommendations of the Cochrane Collaboration and the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15). The protocol was registered on the PROSPERO registry (CRD42024538110). The Cochrane Library, Embase, and PubMed websites were searched. The search included studies published through March 24, 2024, written in English, using the following search terms: "Brain injury," "Brain trauma," "TBI," "Neurostimulant," "1-aminoadamantane," "AmantaHCIAZU," and "PMSAmantadine." In addition, the references of included studies and systematic reviews were screened for additional relevant studies. The complete search strategy is available in the Supplementary material. Two authors independently extracted the data following predefined search criteria and extracted data to a standardized spreadsheet. Disagreements between these authors were resolved through consensus.

2.3 Endpoints and subanalyses

The primary outcomes assessed were Glasgow Coma Scale (GCS), Mini Mental State Examination (MMSE), and DRS, while secondary outcomes included Glasgow Outcome Scale (GOS), mean time on mechanical ventilation (MTMV), and length of hospital stay (LHS). All six outcomes were compared using mean and standard deviation (SD). For DRS, subgroup analyses were performed according to duration of treatment.

2.4 Quality assessment

Quality assessment of RCTs was performed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, in which studies are scored as high, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting biases. We planned to investigate publication bias with funnel plot analysis of the primary outcomes.

2.5 Statistical analysis

This systematic review and meta-analysis was performed in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines (15). Mean differences with a 95% confidence interval was used for continuous comparisons. Heterogeneity was assessed using the Cochrane Q test and the Tau statistic and $I^2 > 25\%$ considered significant. The leave-one-out test was used to assess potential individual study bias. Given the heterogeneity of countries of origin and differences in protocols, the random effects model was used for all studies. The statistical analysis was performed using the R 4.3.2 software. The effect-size was calculated for DRS and GCS.

3 Results

3.1 Study selection and characteristics

As detailed in Figure 1, the initial search yielded 1,292 results. After removal of duplicate records and ineligible studies, 24 remained and were fully reviewed based on inclusion criteria. Of these, a total of 6 RCTs were included, comprising 426 patients, 5 of those being

Abbreviations: GCS, Glasgow Coma Scale; DRS, Disability Rating Scale; MMSE, Mini-Mental State Examination; GOS, Glasgow Outcome Scale; LHS, Length of Hospital Stay; MTMV, Mean Time on Mechanical Ventilation.

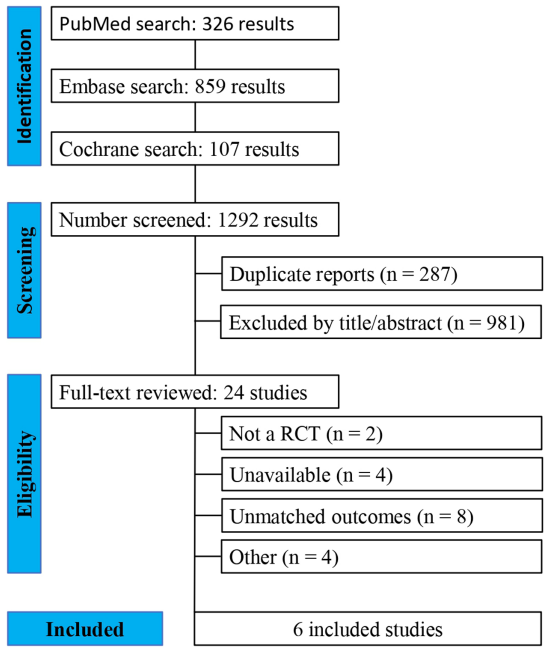

FIGURE 1
PRISMA flow diagram of study screening and selection.

parallel RCTs (10, 13, 16–18) and 1 being a randomized cross-over trial (12). A total of 205 (48.12%) patients received amantadine and 221 (51.88%) received placebo. Additional characteristics of the studies are reported in Table 1.

3.2 Pooled analysis of all studies

Patients receiving amantadine had significantly increased GCS at day 7 (MD 1.50; 95% CI 0.08–2.92; $p = 0.038$; $I^2 = 68\%$; Figure 2) and higher MMSE score (MD 3.23; 95% CI 0.53–5.94; $p = 0.019$; $I^2 = 0\%$; Figure 3). There was no statistically significant difference between groups in terms of GCS at day 3 (MD 0.30; 95% CI -0.49-1.09; $p = 0.452$; $I^2 = 0\%$, Figure 4), DRS (MD −0.50; 95% CI −4.17–3.17; $p = 0.789$; $I^2 = 86\%$, Figure 5) and GOS (MD −0.13; 95% CI −0.37–0.12; $p = 0.320$; $I^2 = 0\%$, Figure 6). The pooled analysis showed no significant difference in hospital length of stay (MD −1.02; 95% CI -6.43-4.39; $p = 0.712$; $I^2 = 0\%$; Figure 7) and mean time on mechanical ventilation (MD −3.13; 95% CI −8.99-2.73; $p = 0.295$; $I^2 = 0\%$; Figure 8) between groups.

3.3 Subgroup analysis

A subgroup analysis was performed in the DRS domain in order to analyze the heterogeneity expressed as I^2 of 86%. For this purpose, the 4 studies used were divided into 2 groups: those whose treatment lasted 3–4 weeks (12, 13) and those whose treatment lasted 6 weeks (10, 16). As result, the DRS analysis between weeks 3 and 4 was not significant and heterogeneity remained high ($I^2 = 76\%$). The analysis at week 6 showed $I^2 = 0\%$ and a mean of 2.40 with 95% CI 0.61–4.20. Both results are shown in Figure 5.

3.4 Quality assessment

Individual RCT appraisal is reported in Supplementary Figures 1, 2. Two studies were considered as overall "low-risk" of bias (13, 18). Four studies were considered to have "some concerns" for bias in the domain 1 (randomization) and 5 (protocol) (10, 12, 16, 17). The funnel-plot analysis was not performed due to poor sensitivity in the setting of a small number of included studies (<10).

The leave-one-out analysis of DRS found high heterogeneity within each iteration when sorted by I^2 (Figure 9) and no significant effect size changes were observed (Figure 10). For GCS at 7 days, leave-one-out analysis shown $I^2 = 0\%$ (Figure 11) and significantly higher effect size favoring patients being treated with amantadine (Figure 12) when Abbasivash et al. study was removed.

4 Discussion

In this systematic review and meta-analysis of 6 studies and 426 patients, we compared amantadine with placebo. Major findings included: (1) significantly increased GCS at 7 days in patients receiving amantadine; (2) higher MMSE score compared to placebo; (3) better DRS between 3rd and 4th week in favor of the placebo group; (4) and no significant differences between groups in terms of GOS, LHS, and MTMV.

A 2022 observational study (19) showed that the use of amantadine significantly improved the GCS of patients with TBI compared to those who did not use it, by more than 3 points at day 5 and at day 10. The GCS is a measure of consciousness used to objectively describe the severity of injury through the patient's level of consciousness, which is clinically interpreted as the quality of the patient's motor, eye, and speech responses (20). The scale analyzes aspects of responsiveness to classify the patient from 3 (worst) to 15 (best). In this study, the GCS was analyzed at two time points according to the information available in the primary studies: on day 3 and day 7 after the start of drug therapy. The difference between the results of the amantadine and control groups was not significant on day 3, but was significant on day 7. This result may be explained by the short duration of treatment on day 3, which is probably insufficient for the drug to show significant results, but also by the fact that the analysis was performed using only two studies, in contrast to the GCS on day 7, which was analyzed using three studies and may have been significant due to the longer time elapsed since the start of treatment. This result is probably due to amantadine acting on the areas responsible for regulating wakefulness, activation, and attention. The drug acts by increasing dopamine in the substantia nigra and neurotransmission within the limbic and frontal mesencephalic system of the striatum (13).

Although significant, the GCS on day 7 deserves some consideration. The I^2 of the result was 68%, high for the parameters chosen for this study. A statistical validation was performed through a leave-one-out test using the studies, following the recommendation of Willis et al. (21) by removing one of the studies from the analysis at a time to investigate which study was accountable for the high heterogeneity of the results. When the Abbasivash study was removed, the heterogeneity was reduced to 0%, the test for overall effect yielded a p-value <0.0001, and the result remained significant, as shown in Figure 9. To ensure greater robustness to the analysis of GCS on day 7, the data available in the Abbasivash study

TABLE 1 Baseline characteristics of included studies.

Study	Design	Patients A/P	Age gap	Age[†], y A/P	Male, % A/P	Treatment protocol	Daily dose*	Routes of administration	Measured outcomes
Abbasivash 2019 (17)	RCT	33/33	NA	39.6/35.8	66.7/72.7	Until discharge, death or complication	200 at firsts 3 days / 400 after 3rd day	Oral	GOS LHS MTMV
Ghalaenovi 2018 (10)	RCT	19/21	(16–80)	32.2/41	100/85.7	6 weeks	100 twice daily	NA	DRS GOS MMSE LHS
Giacino 2012 (13)	RCT	87/97	(16–65)	35.5/37.2	74/71	4 weeks	200 at firsts 14 days / 300 until week 3 / 400 until week 4[&]	Oral or nasogastric	DRS CRS-R
Meythaler 2002 (12)	Cross-over RCT	15/20	(16–75)	NA	NA	6 weeks	100 twice daily	NA	DRS GOS MMSE
Shafiee 2022 (18)	RCT	22/22	(15–75)	40.7/47.4	68.2/68.2	8 days	200	Oral	GCS GOS LHS MTMV
Shimia 2023 (16)	RCT	29/28	NA	NA	NA	6 weeks	100 BD for 14 days; 150 BD for 7 days; 200 BD for 21 days.	NA	DRS GOS

[†]mean; *milligrams; [&]If DRS Score does not fall at least 2 points; A, amantadine; BD, twice a day; NA, not available; P, placebo; RCT, randomized controlled trial; y, years; GCS, Glasgow Coma Scale; LHS, length of hospital stay; MTMV, mean time on mechanical ventilation; DRS, disability rating scale; GOS, Glasgow Outcome Scale; MMSE, Mini-Mental State Examination; CRS-R, Coma Recovery Scale-Revised.

10.3389/fneur.2024.1444623

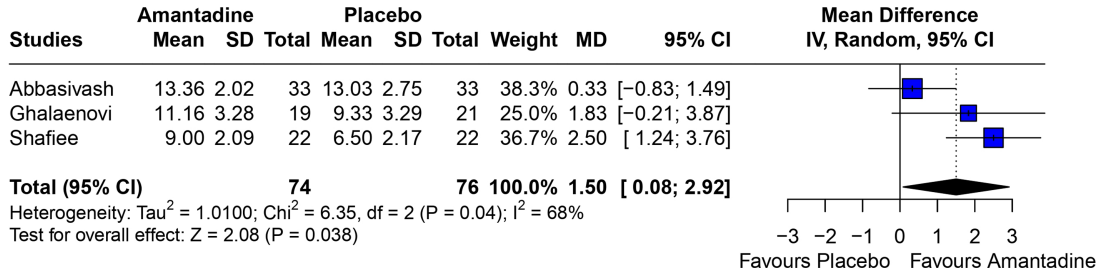

FIGURE 2
At 7 days, mean GCS was significantly higher in patients receiving amantadine as compared with placebo.

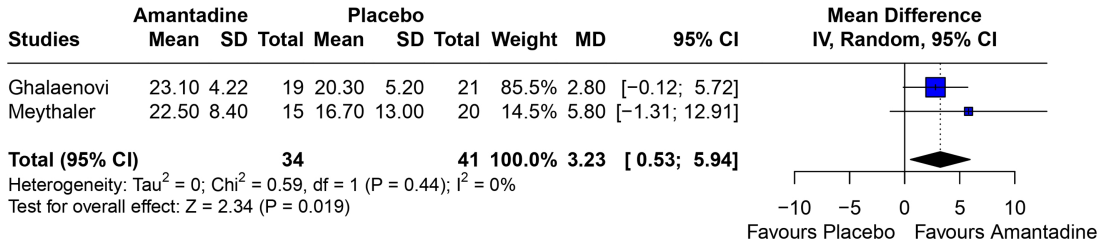

FIGURE 3
MMSE was significantly higher in patients receiving amantadine as compared with placebo.

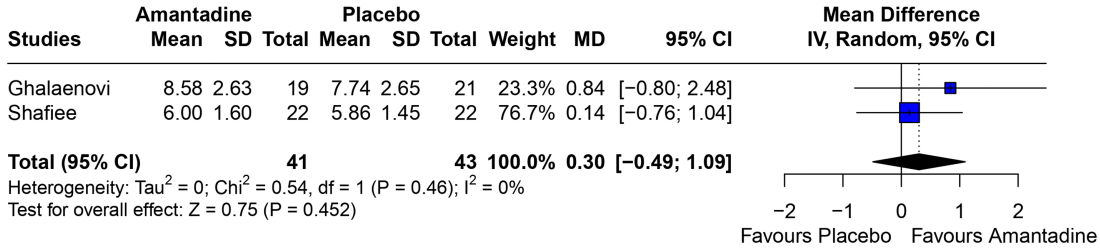

FIGURE 4
At 3 days, there was no significant difference between groups regarding GCS.

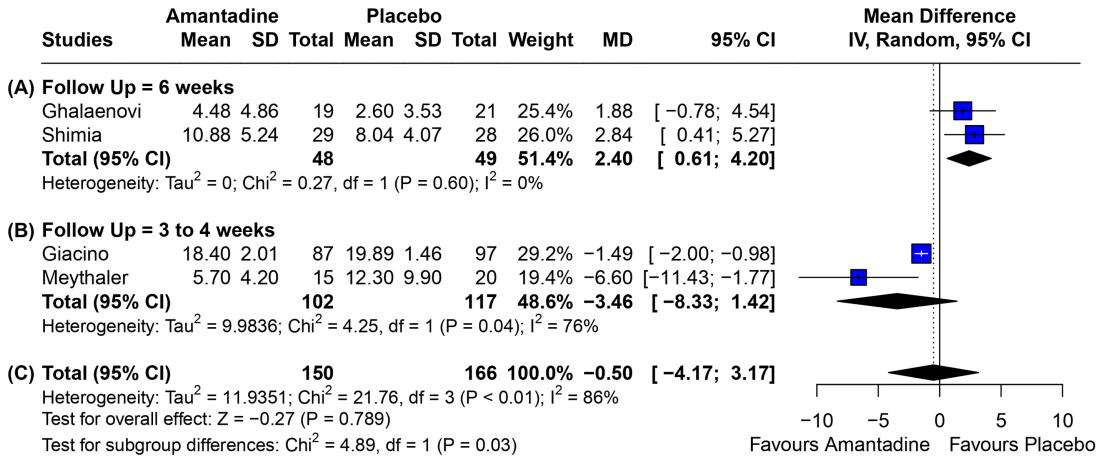

FIGURE 5
Regarding DRS, **(A)** at 6 weeks of follow-up, there was a significant benefit for patients receiving amantadine; **(B)** at 3–4 weeks of follow-up, there was no difference between groups; and **(C)** on overall analysis regardless of follow-up time, there was no significant difference between patients being treated with amantadine and placebo.

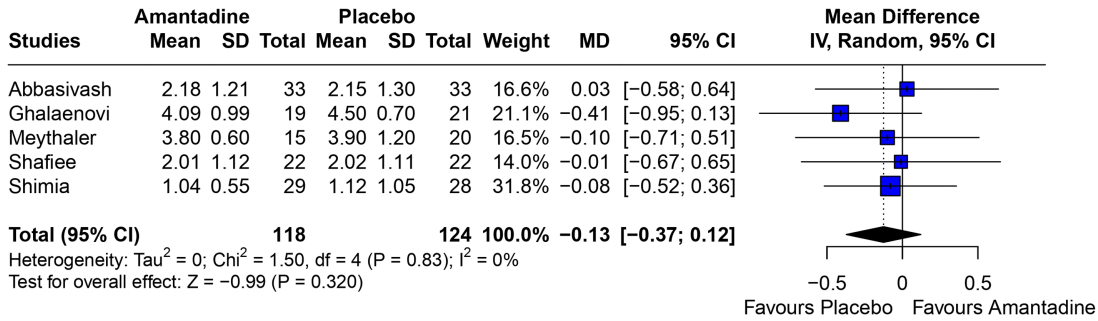

FIGURE 6
There was no significant difference between groups regarding GOS.

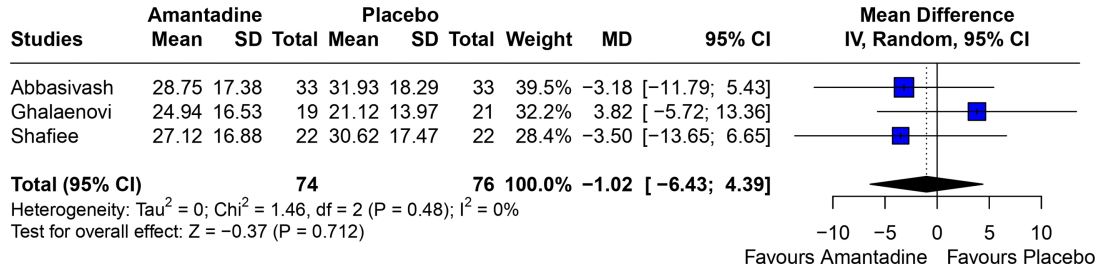

FIGURE 7
There was no significant difference in the length of hospital stay in patients receiving amantadine versus placebo.

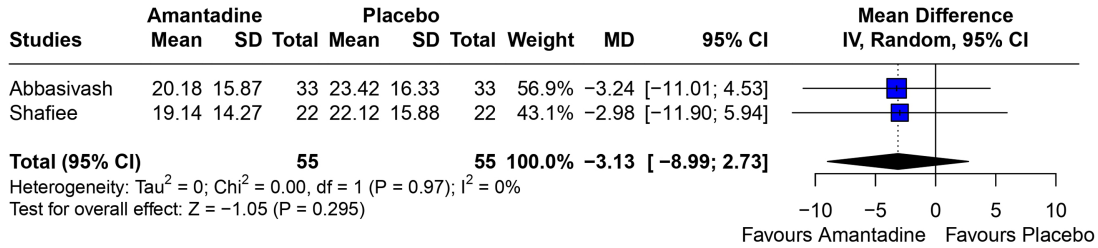

FIGURE 8
Neither group had a significant advantage in mean time on mechanical ventilation.

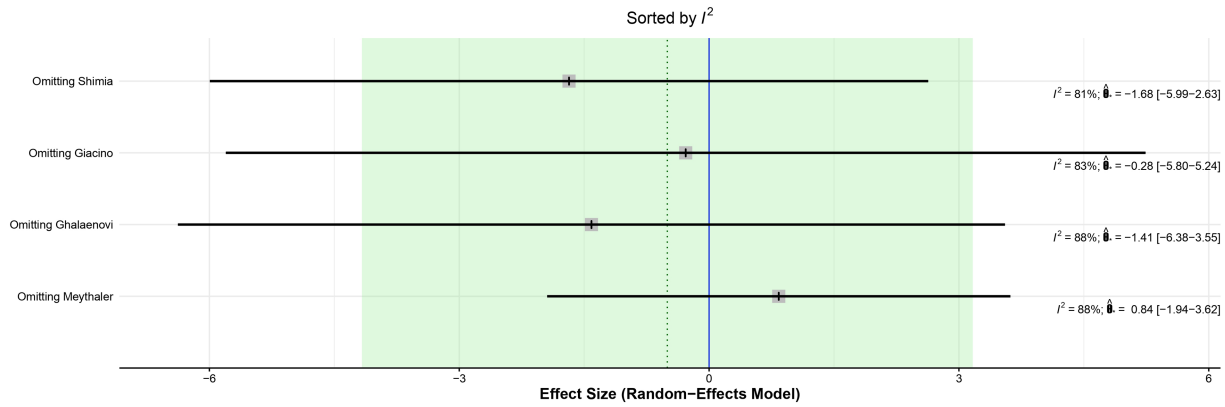

FIGURE 9
Heterogeneity remained high in all iterations on leave-one-out analysis sorted by I^2 of DRS.

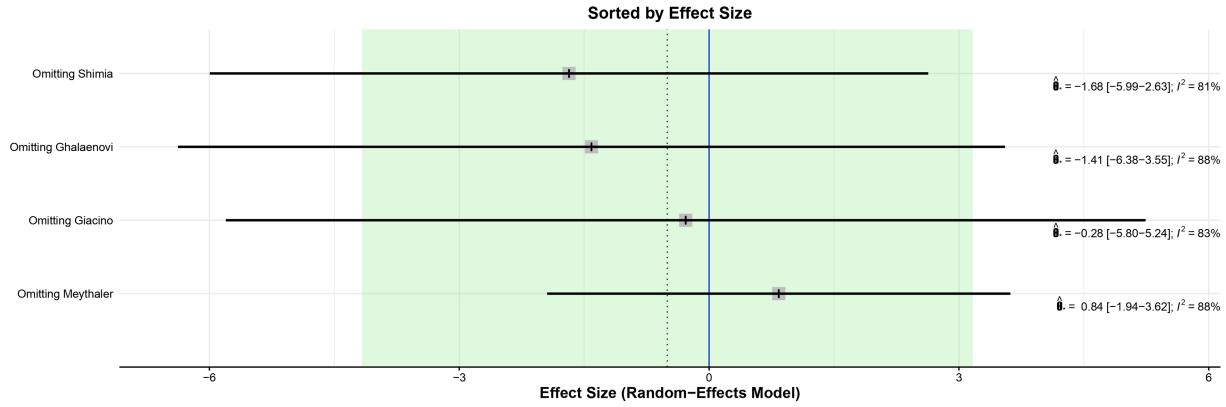

FIGURE 10
Leave-one-out analysis of DRS sorted by effect size found no significant effect size changes.

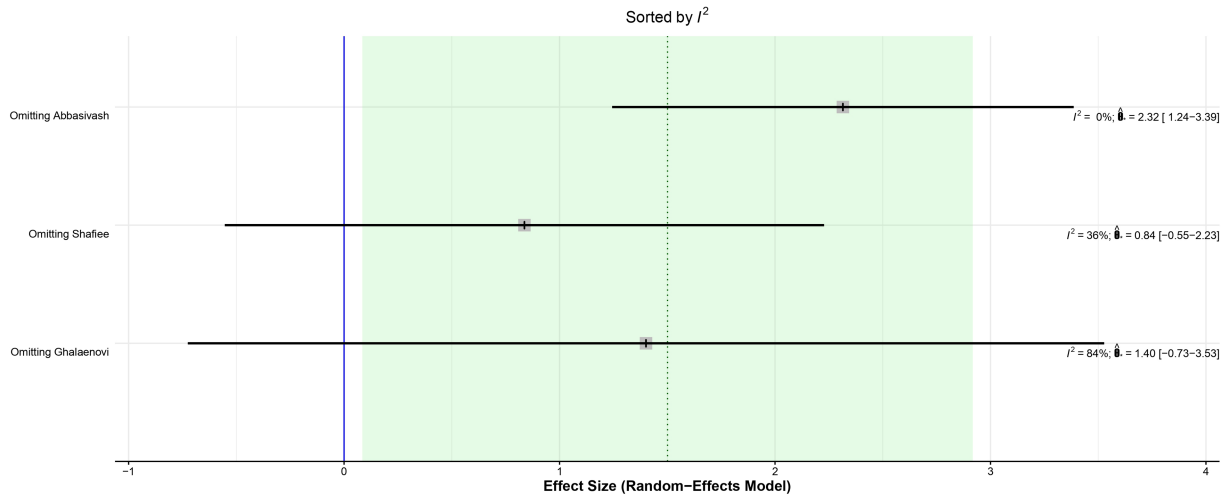

FIGURE 11
The heterogeneity was reduced to I^2 = 0% when the Abbasivash et al. study was removed.

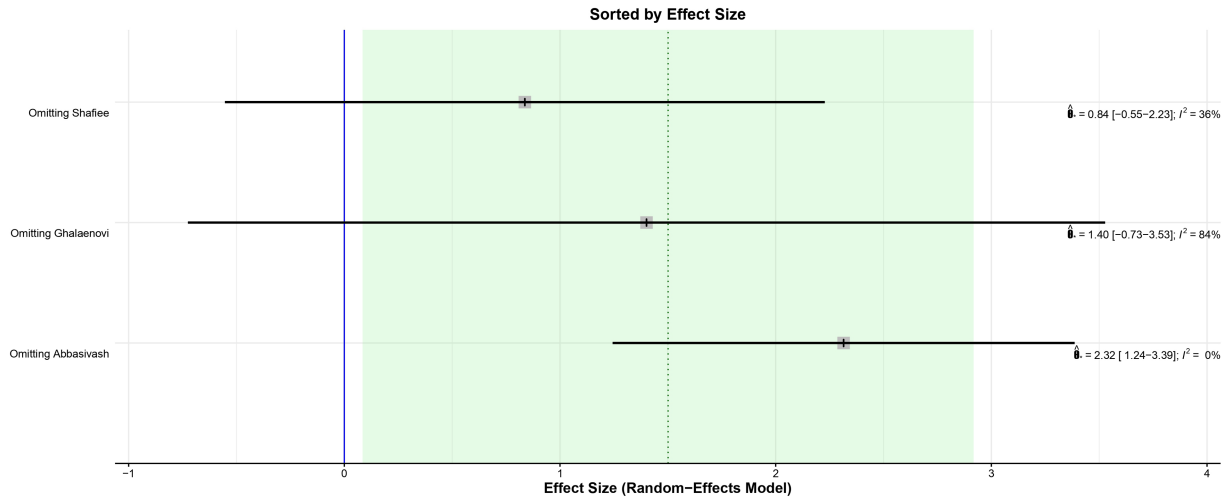

FIGURE 12
Leave-one-out analysis of GCS at 7 days sorted by effect size showed a statistically significant benefit for patients treated with amantadine when the Abbasivash et al. study was removed.

were included, although they correspond to day 13.73 (mean). This decision may have biased the result due to the time of outcome assessment variability within the primary studies. It must be noted that GCS has been used to assess the level of consciousness, although it does not provide a comprehensive view of overall brain function. In this sense, its use can be influenced not only by the primary clinical condition, but also by associated traumatic injuries, cardiac and/or respiratory complications, and previous conditions. Additionally, the use of sedatives or analgesics during treatment also may alter GCS. These considerations are relevant to all observations based on GCS (22).

The MMSE is used as a diagnostic tool to evaluate cognitive impairment in patients with TBI and studies suggest it might be a good predictor of rehabilitation (23, 24). Retrospective studies on patients with moderate to severe TBI found that MMSE had a correlation of −0.707 with DRS at discharge (24) and a higher Modified Barthel Index after rehabilitation (23). However, contrary to those studies, our analysis have shown a significantly higher MMSE and a higher DRS at 6 weeks follow-up on patients treated with amantadine. Although the treatment duration of the patients included in Meythaler's study was half that of Ghalaenovi's study, both analyses tended to favor the amantadine group, and together they form a significant result. In addition, both studies included patients with the same admission GCS (< 10), the sample of both studies was very close, and all other relevant details of the studies were similar, minimizing the bias of this analysis.

An observational study of 124 patients showed that amantadine has the ability to improve DRS (25). In addition, a 2023 study by Tracy et al., with 55 patients, confirmed the benefit of amantadine in DRS (26). Additionally, a previous meta-analyses also found a significant functional improvement in TBI patients treated with amantadine (27). Nonetheless, there was high heterogeneity due to different outcome measures (such as DRS, GCS and GOS) and no subgroup analyses regarding different follow-up time points. The results of our analysis were not consistent with their findings and had high heterogeneity. Although amantadine showed a positive impact on GCS, it seems not to have a significant long-term effect on cognition and functionality. The concept of cognition is broad and involves memory, planning, visual–spatial recognition, and other aspects (28). In our subanalysis, after 6 weeks of follow-up, there was a significant improvement in functionality (as measured by DRS) for patients in the placebo group, indicating that amantadine may be related to worse long-term outcomes regarding cognition and functionality. We hypothesize that although amantadine may accelerate the awakening of patients through the enhancement of dopamine in the substantia nigra and in neurotransmission within the mesencephalic limbic and frontal striatum loop system, this earlier recovery might be associated with a worse cognitive and functional outcome. One of the pathophysiological mechanisms that may be related to this hypothesis is that the blockade of synaptic transmission promoted by NMDA antagonists might hinder neuronal survival at longer follow-up time points, partly due to off-target neurotoxicity and the effects of inhibiting normal neuroplasticity and synaptic function (29–31). Perhaps, this discrepancy can be also explained by the methodological difference between our analysis and the previous studies. In our study, only RCTs were used for the analysis, which have a significantly lower possibility of bias than observational studies. In addition, 4 studies were used for the analysis, which increases the statistical power due to the larger number of patients compared to single observational studies. Moreover, we attempted to explore heterogeneity with a subgroup analysis by time of follow-up and using leave-one-out test. As a result, the subanalysis of studies that treatment lasted for 6 weeks showed a favorable result for the placebo group. However, the subanalysis at weeks 3 and 4 was not significant and heterogeneity remained high. The heterogeneity remained high even within the leave-one-out test. Whyte et al. theorize that the difference in the final outcome of DRS can be explained by the difference in the time it takes to transfer patients to the hospital. Those who were transferred earlier tended to have a better prognosis and leave the hospital sooner. Therefore, the studies with up to 6 weeks of follow-up may have included patients who were admitted later, had a worse prognosis, and therefore stayed in the hospital longer than in the studies with 3–4 weeks of follow-up. Thus, the advantage of the placebo group may actually be due to a bias in the severity of the patients included.

In a previous 11 year propensity matched retrospective analysis comparing use of amantadine or standard treatment in patients with severe traumatic brain injury, patients receiving amantadine were less likely to have favorable recovery (measured by GCS at discharge) and had a longer LHS (32); however, our findings based on RCTs did not find a significant difference between groups in GOS or length of hospital stay. Additionally, the pooled analysis showed no difference in MTMV.

Our study has some limitations. First, a cross-over trial was pooled with non-crossover RCTs to increase the statistical power of the analysis. To mitigate the potential bias of this pooling, the results of the additional cross-over trial were considered only up to the start of the washout period to avoid carry-over effect, even though this shortens treatment duration. Second, the authors did not obtain the full Shimia article and used the information in the abstract as the basis for this study. To minimize the bias of this choice, they used the information from Shimia's paper that was available from previous studies that had also used it. There was variability within the studies on the severity of TBI and medication dosage, which might partially explain high heterogeneity found on GCS at 7 days and DRS; leave-one-out analysis and subgroup analysis were performed to address this issue. No significant differences were found on leave-one-out analysis sorted by effect size (Figures 11, 12). In addition, systematic reviews have inherent limitations and are susceptible to publication bias, language bias, bias in primary studies, bias from combining studies with relatively different populations, comparison of outcomes, and definition of outcomes.

5 Conclusion

This meta-analysis of 426 TBI patients demonstrated the efficacy of amantadine in improving cognition compared with placebo. The improvement in patients' level of consciousness as measured by the GCS and the MMSE was significantly greater in those who used amantadine compared with placebo. However, the improvement in the DRS between the 3rd and 4th week of treatment was more favorable for patients in the placebo group. Altogether, these findings suggest a good theoretical basis for selecting amantadine as a good drug for reversing cognitive damage after TBI, with the addendum that the drug performs worse on some scales.

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

JF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AH: Data curation, Writing – review & editing. AP: Data curation, Writing – review & editing. SC: Funding acquisition, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This article was supported by Faculdade de Medicina da Universidade Federal do Pará (FAMED -UFPA) and Pró-Reitoria de Pesquisa e Pós-Graduação (PROPESP).

Acknowledgments

We would like to acknowledge the "Faculdade de Medicina da Universidade Federal do Pará" (FAMED - UFPA) and "Pró-Reitoria de Pesquisa e Pós-Graduação" (PROPESP) for the financial support regarding publication fees.

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

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 24 April 2025
DOI 10.3389/fneur.2025.1448439

OPEN ACCESS

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RECEIVED 13 June 2024
ACCEPTED 04 April 2025
PUBLISHED 24 April 2025

CITATION
Gao S, Zhu Z and Zheng W (2025) Thiamine administration and in-hospital mortality in patients with traumatic brain injury: analysis of the MIMIC-IV database.
Front. Neurol. 16:1448439.
doi: 10.3389/fneur.2025.1448439

Thiamine administration and in-hospital mortality in patients with traumatic brain injury: analysis of the MIMIC-IV database

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Aim: Several studies have suggested the favorable impact of thiamine administration on the prognosis of diseases. However, the value of thiamine in patients with traumatic brain injury (TBI) admitted to the intensive care unit (ICU) remains unclear. The aim of this study was to investigate the association between the between thiamine administration and in-hospital mortality in TBI patients.

Methods: A cohort of 1,755 individuals diagnosed with TBI from the Medical Information Mart for Intensive Care IV database were included in this retrospective cohort study. Thiamine administration is determined by the patient's usage during their stay in the ICU. The primary outcome was in-hospital mortality. Univariable and multivariable Cox regression analysis were used to investigate the relationship between thiamine administration and in-hospital mortality of patients with TBI. Subgroup analysis was also performed to determine if this association differed for subgroups classified using different variables including age (<65 years and ≥65 years), gender (male and female), and the severity of TBI (mild, moderate, and severe).

Results: The median follow-up time was 6.77 (3.98, 12.94) days, and the in-hospital mortality rate for the population was approximately 14.1%. In the univariable Cox regression analysis, thiamine administration was significantly associated with the reduced risk of in-hospital mortality in TBI patients admitted to the ICU. performing the multivariable Cox regression analysis, the observed association of thiamine administration and in-hospital mortality remained significant, with the hazard ratios (HR) of 0.66 [95% confidence interval (CI) = 0.45–0.98]. In the subgroup analysis, the results demonstrated that thiamine administration resulted in a decreased risk of in-hospital mortality among TBI patients who aged 65 years or older (HR = 0.36, 95% CI: 0.19–0.69), as well as male individuals (HR = 0.36, 95% CI: 0.17–0.80) and those with severe TBI (HR = 0.16, 95% CI: 0.04–0.57).

Conclusion: Thiamine administration may reduce in-hospital mortality for patients with TBI admitted to the ICU.

KEYWORDS

thiamine, traumatic brain injury, in-hospital mortality, intensive care unit, Medical Information Mart for Intensive Care IV

Introduction

Traumatic brain injury (TBI) is regarded as an acquired insult to the brain resulting from external mechanical force, which might lead to potential temporary or permanent impairment (1, 2). The research findings indicate that TBI has been a prominent contributor to global disability, morbidity, and mortality (3). High mortality rate of TBI is attributed not only to the severity of the initial brain injury, but also to systemic complications arising as a result of the brain injury (4, 5). Despite the gradual improvement and standardization of treatment options, the mortality associated with TBI remains a cause for concern, Therefore, exploring the new therapeutic approaches is crucial for improving the prognosis of TBI patients.

Thiamine is an essential water-soluble vitamin that plays a crucial role in various physiological processes (6). Thiamine deficiency may result in alterations in neurotransmitters, lactic acidosis, apoptosis, activation of oxidative stress response, inflammation, as well as dysfunction of the blood–brain barrier (7, 8). In the pathophysiology of TBI, the increasing of free radical and reactive oxygen species following the injury results in oxidative stress and subsequent secondary neurotoxicity (9). An animal experiment demonstrated that thiamine has the potential to effectively ameliorate mitochondrial damage and neuritis in rats with TBI (10). A retrospective cohort analysis revealed that thiamine was linked with decreased risk of in-hospital mortality among heart failure patients admitted to the intensive care unit (ICU) (11). Early thiamine administration was found to have an improvement in short-term survival outcomes for critically ill patients with acute kidney injury (AKI) (12). In addition, the study conducted by Yue et al. also highlighted a significant reduction in the risk of in-hospital, 30-day, and 90-day mortality among myocardial infarction patients receiving thiamine compared to those not receiving thiamine (13). These studies findings suggested the favorable impact of thiamine administration on the prognosis of diseases. However, the existing studies does not provide any evidence regarding the potential effect of thiamine in enhancing outcomes among critically ill individuals suffering from TBI.

Therefore, this study intends to investigate the association between thiamine administration and the risk of in-hospital mortality in patients with TBI based on Medical Information Mart for Intensive Care (MIMIC)-IV database. The findings from this research might provide valuable insights for treatment decision-making and prognosis enhancement in TBI patients.

Methods

Study population

This retrospective cohort study obtained all data from the MIMIC-IV, an openly accessible and freely available critical care database (14). This database contained comprehensive clinical data of patients who underwent inpatient treatment at the Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019, such as basic patient information, vital signs, laboratory indicators and survival data. We did not require patient consent or ethical approval as all patient privacy information in the database has been de-identified.

We selected patients from the MIMIC-IV database based on the following criteria: (1) diagnosed as TBI at ICU admission [International Classification of Disease, Ninth (ICD-9: 85) and Tenth (ICD-10: S06) Versions]; (2) aged≥18 years old. The exclusion criteria for participation in the study were as follows: (1) hospitalized in the ICU for less than 24 h (n = 626); (2) missing information of thiamine use (n = 0); (3) missing survival information (n = 1). The flowchart for study participants enrolling is presented in Figure 1.

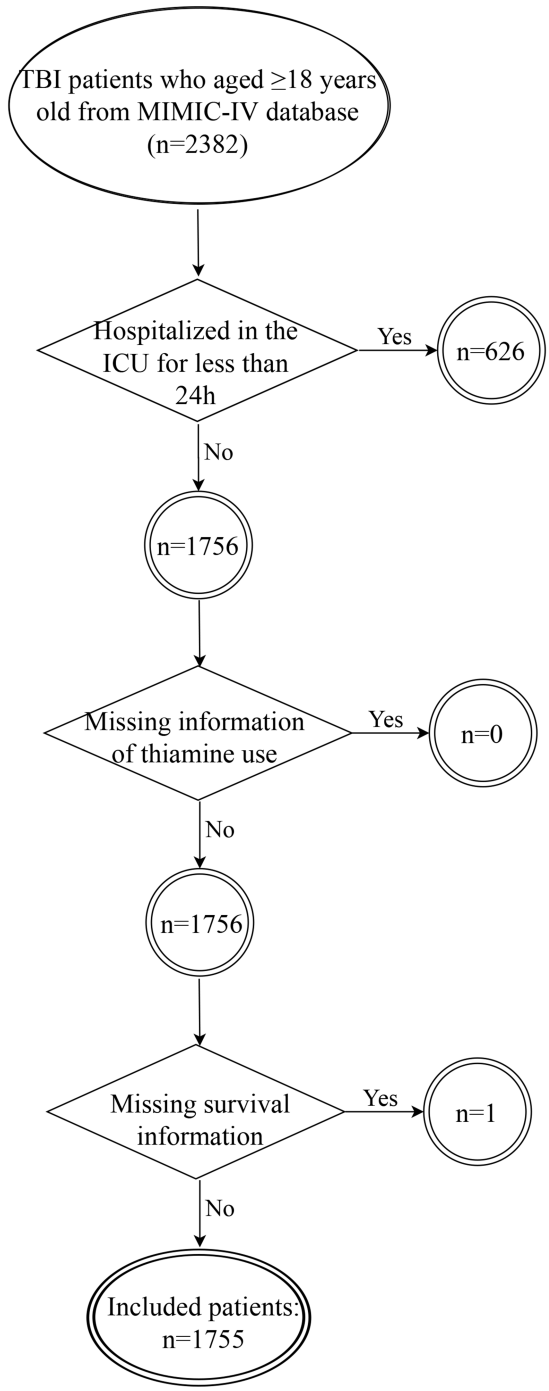

FIGURE 1
Flowchart for study participants enrolling.

Data collection

We extracted some important variables from the MIMIC-IV database: age (years), gender, race/ethnicity, insurance status, ICU type, urine output (mL), hypertension, deterioration of neurological function, acute kidney injury (AKI), heart rate (bpm), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), respiratory rate (insp/min), temperature (°C), oxygen saturation (SpO_2, %), Sequential Organ Failure Assessment (SOFA) score, Charlson comorbidity index (CCI), Glasgow Coma Score (GCS), Simplified Acute Physiology Score II (SAPSII), white blood cell (WBC, K/μL), platelet (K/μL), hemoglobin (g/dL), hematocrit (%), red cell distribution width (RDW, %), epidermal growth factor receptor (eGFR, mL/min/1.73m^2), blood urea nitrogen (BUN, mg/dL), glucose (mg/dL), calcium (mg/dL), sodium (mEq/L), potassium (mEq/L), chloride (mEq/L), vasopressor, mechanical ventilation, mannitol, diuretic, surgery, and thiamine. Deterioration of neurological function was defined as a decline of ≥2 points in the GCS during the ICU period (15). Thiamine administration is determined by the patient's usage during their stay in the ICU. The primary outcome of the present study was in-hospital mortality. For patients with multiple ICU admissions, only clinical data from the first ICU admission were utilized. Variables with more than 10% missing values were excluded from the study. Conversely, these variables with less than 10% missing values were imputed using multiple interpolation method. Supplementary Table 1 shows the sensitivity analysis on the data sets before and after interpolation.

Statistical analysis

We reported the categorical variables as numbers and percentages. The normally distributed continuous variables were expressed as the means ± standard deviation (SD), the skewed distributed continuous variables as the median and interquartile range [M (Q_1, Q3)]. Among the groups, we compared categorical variables by Chi-squared test. Continuous variables were compared by T test (normally distributed) or Wilcoxon rank sum test (skewed distributed). Univariable and multivariable Cox regression analysis were used to investigate the relationship between thiamine administration and in-hospital mortality of patients with TBI, the results were expressed as hazard ratios (HR) and 95% confidence interval (CI). Model 1 was unadjusted (univariable Cox regression analysis). Model 2 (multivariable Cox regression analysis) adjusted for all confounding variables. $p < 0.05$ was considered statistically significant. Subgroup analysis was also performed to determine if this association differed for subgroups classified using different variables including age (<65 years and ≥ 65 years), gender (male and female), and the severity of TBI (mild, moderate, and severe). According to the GCS, patients with TBI can be categorized as mild (13–15 points), moderate (9–12 points), or severe (3–8 points) (16). In addition, Kaplan–Meier survival curves were employed to observe the relationship between thiamine administration and in-hospital mortality among patients with TBI. All statistical analyses were performed using SAS9.4 software.

Results

General characteristics

A total of 1,755 individuals diagnosed with TBI were included in this study, with an average age of 64.41 ± 20.26 years. Among them, 1,079 (61.48%) patients were men. The median follow-up time was 6.77 (3.98, 12.94) days, and the in-hospital mortality rate for the population was approximately 14.1%. Table 1 summarizes the comparison of characteristics between the survival (n = 1,538) and in-hospital mortality groups (n = 217). Compared with the survival group, the in-hospital mortality group showed older age (70.25 vs. 63.59 years, $p < 0.001$), higher prevalence of deterioration of neurological function (62.21% vs. 51.04%, $p = 0.002$) and AKI (80.65% vs. 54.68%, $p < 0.001$) but lower DBP, temperature, platelet, hematocrit, hemoglobin, eGFR, and calcium levels ($p < 0.05$). In addition, we also observed that the proportion of thiamine use in the in-hospital mortality group (16.13%) was lower than that of the survival group (21.65%^), although without statistical significance. The detailed population characteristics can be found in Table 1.

Thiamine administration and in-hospital mortality

Univariable Cox regression identified 21 variables significantly linked to mortality ($p < 0.05$), including age (HR = 1.02, 95% CI: 1.02–1.03), AKI (HR = 1.96, 95% CI: 1.40–2.76), and SOFA score (HR = 1.21, 95% CI: 1.14–1.28), protective factors included hemoglobin (HR = 0.90, 95% CI: 0.84–0.95) and temperature (HR = 0.75, 95% CI: 0.67–0.84), as presented in Supplementary Table 2. These variables were subsequently adjusted in multivariable models to isolate the independent effect of thiamine on mortality. In both unadjusted and adjusted Cox regression analyses, we found that thiamine administration was significantly associated with the reduced risk of in-hospital mortality in TBI patients admitted to the ICU (Model 1: HR = 0.46, 95% CI: 0.32–0.67, $p < 0.001$; Model 2: HR = 0.66, 95% CI: 0.45–0.98, $p = 0.037$). Kaplan–Meier survival curves (Figure 2) suggested that the survival rate of thiamine administration group was significantly higher than that of the non-thiamine administration group ($p < 0.001$). The thiamine group demonstrated higher cumulative survival rates over the follow-up period (median: 6.77 days), aligning with regression results (Table 2).

Subgroup analysis

We performed subgroup analysis based on age (<65 years and ≥ 65 years), gender (male and female), and the severity of TBI (mild, moderate, and severe) to assess the association between thiamine administration and in-hospital mortality in TBI patients admitted to the ICU (Table 3). After performing the multivariable Cox regression analysis, the results demonstrated that thiamine administration resulted in a decreased risk of in-hospital mortality among TBI patients who aged 65 years or older (HR = 0.36, 95% CI: 0.19–0.69, $p = 0.002$), as well as male individuals (HR = 0.36, 95% CI: 0.17–0.80,

10.3389/fneur.2025.1448439

TABLE 1 Comparison of characteristics between the survival and in-hospital mortality groups.

Variables	Total (*n* = 1,755)	Survival group (*n* = 1,538)	In-hospital mortality group (*n* = 217)	Statistics	*p*
Age (years), Mean ± SD	64.41 ± 20.26	63.59 ± 20.37	70.25 ± 18.52	t = −4.56	<0.001
Gender, *n* (%)				χ^2 = 1.572	0.210
Female	676 (38.52)	584 (37.97)	92 (42.40)		
Male	1,079 (61.48)	954 (62.03)	125 (57.60)		
Race, *n* (%)				χ^2 = 18.978	<0.001
White	1,110 (63.25)	999 (64.95)	111 (51.15)		
Black	108 (6.15)	96 (6.24)	12 (5.53)		
Other	537 (30.60)	443 (28.80)	94 (43.32)		
Insurance, *n* (%)				χ^2 = 14.976	<0.001
Medicaid	122 (6.95)	105 (6.83)	17 (7.83)		
Medicare	740 (42.17)	624 (40.57)	116 (53.46)		
Other	893 (50.88)	809 (52.60)	84 (38.71)		
ICU type, *n* (%)				χ^2 = 3.394	0.335
MICU	102 (5.81)	84 (5.46)	18 (8.29)		
SICU	463 (26.38)	405 (26.33)	58 (26.73)		
TSICU	762 (43.42)	668 (43.43)	94 (43.32)		
Other	428 (24.39)	381 (24.77)	47 (21.66)		
Urine output (mL), M (Q_1, Q_3)	1632.00 (1070.00, 2310.00)	1631.00 (1085.00, 2290.00)	1670.00 (1005.00, 2425.00)	Z = 0.408	0.683
Hypertension, yes, *n* (%)	912 (51.97)	791 (51.43)	121 (55.76)	χ^2 = 1.428	0.232
Deterioration of neurological function, yes, *n* (%)	920 (52.42)	785 (51.04)	135 (62.21)	χ^2 = 9.516	0.002
AKI, yes, *n* (%)	1,016 (57.89)	841 (54.68)	175 (80.65)	χ^2 = 52.588	<0.001
Heart rate (bpm), Mean ± SD	84.83 ± 18.53	84.56 ± 18.16	86.76 ± 20.91	t = −1.48	0.141
SBP (mmHg), Mean ± SD	132.73 ± 22.87	132.93 ± 22.44	131.29 ± 25.71	t = 0.90	0.371
DBP (mmHg), Mean ± SD	72.41 ± 16.98	72.77 ± 16.70	69.86 ± 18.68	t = 2.17	0.031
Respiratory rate (insp/min), Mean ± SD	18.52 ± 5.17	18.44 ± 5.08	19.08 ± 5.80	t = −1.55	0.122
Temperature (°C), Mean ± SD	36.80 ± 0.80	36.83 ± 0.73	36.56 ± 1.16	t = 3.33	<0.001
SPO_2 (%), Mean ± SD	97.52 ± 3.62	97.47 ± 3.62	97.84 ± 3.61	t = −1.41	0.160
SOFA, M (Q_1, Q_3)	1.00 (0.00, 1.00)	0.00 (0.00, 1.00)	1.00 (0.00, 3.00)	Z = 6.719	<0.001
CCI, M (Q_1, Q_3)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 3.00)	Z = 4.308	<0.001
GCS, M (Q_1, Q_3)	14.00 (13.00, 15.00)	14.00 (13.00, 15.00)	15.00 (9.00, 15.00)	Z = 0.147	0.883
SAPSII, M (Q_1, Q_3)	32.00 (25.00, 40.00)	31.00 (24.00, 38.00)	40.00 (33.00, 50.00)	Z = 11.853	<0.001
WBC (K/uL), M (Q_1, Q_3)	10.20 (7.50, 13.20)	10.00 (7.40, 13.00)	11.70 (8.80, 15.00)	Z = 4.905	<0.001
Platelet (K/uL), M (Q_1, Q_3)	189.00 (146.00, 242.00)	190.00 (150.00, 242.00)	174.00 (123.00, 224.00)	Z = -3.209	0.001
Hematocrit (%), Mean ± SD	34.20 ± 5.78	34.41 ± 5.66	32.65 ± 6.38	t = 3.86	<0.001
Hemoglobin (g/dL), Mean ± SD	11.40 ± 2.03	11.49 ± 2.00	10.80 ± 2.15	t = 4.66	<0.001
RDW (%), Mean ± SD	14.23 ± 1.90	14.09 ± 1.75	15.19 ± 2.55	t = −6.12	<0.001
eGFR (mL/min/1.73m^2), Mean ± SD	95.20 ± 14.58	95.60 ± 14.66	92.34 ± 13.66	t = 3.09	0.002
BUN (mg/dL), M (Q_1, Q_3)	15.00 (11.00, 22.00)	15.00 (11.00, 21.00)	18.00 (14.00, 29.00)	Z = 6.330	<0.001
Glucose (mg/dL), M (Q_1, Q_3)	123.00 (102.00, 154.00)	121.00 (101.00, 149.00)	142.00 (114.00, 173.00)	Z = 6.291	<0.001
Calcium (mg/dL), Mean ± SD	8.09 ± 1.48	8.12 ± 1.46	7.88 ± 1.60	t = 2.23	0.026
Sodium (mEq/L), Mean ± SD	138.80 ± 4.90	138.74 ± 4.77	139.25 ± 5.69	t = −1.27	0.207
Potassium (mEq/L), Mean ± SD	4.07 ± 0.71	4.06 ± 0.70	4.14 ± 0.83	t = −1.27	0.207
Chloride (mEq/L), Mean ± SD	103.67 ± 5.70	103.61 ± 5.53	104.10 ± 6.73	t = −1.02	0.307

(Continued)

TABLE 1 (Continued)

Variables	Total (n = 1,755)	Survival group (n = 1,538)	In-hospital mortality group (n = 217)	Statistics	p
Vasopressors, yes, n (%)	228 (12.99)	157 (10.21)	71 (32.72)	χ^2 = 85.252	<0.001
Mechanical ventilation, yes, n (%)	1,166 (66.44)	980 (63.72)	186 (85.71)	χ^2 = 41.260	<0.001
Mannitol, yes, n (%)	49 (2.79)	25 (1.63)	24 (11.06)	χ^2 = 62.366	<0.001
Diuretic, yes, n (%)	338 (19.26)	261 (16.97)	77 (35.48)	χ^2 = 41.918	<0.001
Surgery, yes, n (%)	14 (0.80)	12 (0.78)	2 (0.92)	-	0.688
Thiamine, yes, n (%)	368 (20.97)	333 (21.65)	35 (16.13)	χ^2 = 3.500	0.061
Follow-up-time (days), M (Q_1, Q_3)	6.77 (3.98, 12.94)	6.92 (4.21, 13.45)	5.15 (2.40, 10.46)	Z = -5.175	<0.001

ICU, intensive care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma and surgical intensive care unit; AKI, acute kidney injury; SBP, systolic blood pressure; DBP, diastolic blood pressure; SPO_2, pulse oxygen saturation; SOFA, Sequential Organ Failure Assessment; CCI, Charlson comorbidity index; GCS, Glasgow Coma Score; SAPSII, Simplified Acute Physiology Score II; WBC, white blood cell; RDW, red cell distribution width; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen.

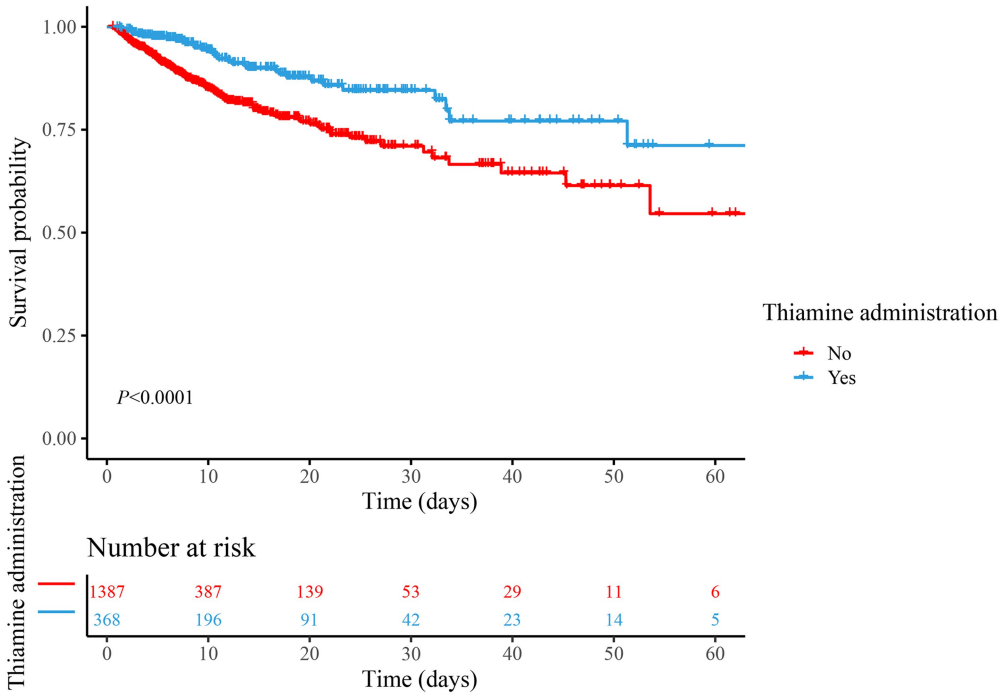

FIGURE 2
Comparison of survival between the thiamine group and the non-thiamine group using the Kaplan–Meier survival analysis in the cohort.

p = 0.012) and those with severe TBI (HR = 0.16, 95% CI: 0.04–0.57, p = 0.005).

Discussion

This retrospective study investigated the therapeutic potential of thiamine supplementation in TBI management using data from the MIMIC-IV database. Our analysis revealed a significant association between thiamine administration and reduced in-hospital mortality risk among critically ill TBI patients (HR = 0.46, 95% CI: 0.32–0.67, p < 0.001). Notably, this mortality reduction remained statistically significant after rigorous adjustment for injury severity, comorbidities, and treatment covariates through multivariable logistic regression modeling (HR = 0.66, 95% CI: 0.45–0.98, p = 0.037). These findings suggest that this readily available micronutrient intervention, characterized by its favorable safety profile and low cost, may represent a novel neuroprotective strategy for improving clinical outcomes in TBI populations requiring intensive care.

The water-soluble vitamin thiamine, commonly known as vitamin B1, is essential for glucose metabolism as its bioactive form, thiamine pyrophosphate, acts as essential co-enzyme (17). Total thiamine levels (essentially TPP) are much lower in humans than other species with a normal steady-state whole body store of approximately 30 mg (18). The Recommended Daily Allowance (RDA) suggests the thiamine dose for adults as 1.1–1.2 mg/day (19). Critically ill patients with TBI often experience exacerbated thiamine deficiency due to heightened metabolic demands, insufficient supplementation, and increased urinary excretion (20). Recently, numerous published studies have suggested the beneficial effects of thiamine supplementation on the

TABLE 2 Thiamine administration and in-hospital mortality.

Variables	Model 1		Model 2	
	HR (95%CI)	*p*	HR (95%CI)	*p*
Thiamine administration				
No	Ref		Ref	
Yes	0.46 (0.32–0.67)	<0.001	0.66 (0.45–0.98)	0.037

Ref, reference; HR, hazard ratio; CI, confidence interval; Model 1: unadjusted; Model 2: adjusted age, gender, insurance status, urine output, acute kidney injury, diastolic blood pressure, temperature, Sequential Organ Failure Assessment, Charlson comorbidity index, Glasgow Coma Score, Simplified Acute Physiology Score II, white blood cell, hematocrit, hemoglobin, red cell distribution width, estimated glomerular filtration rate, blood urea nitrogen, glucose, sodium, vasopressor, mechanical ventilation, and mannitol.

TABLE 3 Subgroup analysis.

Variables	Age: <65		Age: ≥65	
	HR (95%CI)	*p*	HR (95%CI)	*p*
Thiamine administration				
No	Ref		Ref	
Yes	0.71 (0.39–1.27)	0.244	0.36 (0.19–0.69)	0.002

Variables	Gender: male		Gender: female	
	HR (95%CI)	*p*	HR (95%CI)	*p*
Thiamine administration				
No	Ref		Ref	
Yes	0.36 (0.17–0.80)	0.012	0.78 (0.49–1.24)	0.286

Variables	GCS: 13–15 points		GCS: 9–12 points		GCS: 3–8 points	
	HR (95%CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
Thiamine administration						
No	Ref		Ref		Ref	
Yes	0.81 (0.50–1.29)	0.367	0.35 (0.11–1.14)	0.083	0.16 (0.04–0.57)	0.005

Ref, reference; HR, hazard ratio; CI, confidence interval; GCS, Glasgow Coma Score; In age subgroup: adjusted gender, insurance status, urine output, acute kidney injury (AKI), diastolic blood pressure (DBP), temperature, Sequential Organ Failure Assessment (SOFA), Charlson comorbidity index (CCI), GCS, Simplified Acute Physiology Score II (SAPSII), white blood cell (WBC), hematocrit, hemoglobin, red cell distribution width (RDW), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), glucose, sodium, vasopressor, mechanical ventilation, and mannitol. In gender subgroup: adjusted age, insurance status, urine output, AKI, DBP, temperature, SOFA, CCI, GCS, SAPSII, WBC, hematocrit, hemoglobin, RDW, eGFR, BUN, glucose, sodium, vasopressor, mechanical ventilation, and mannitol. In GCS subgroup: adjusted age, gender, insurance status, urine output, AKI, DBP, temperature, SOFA, CCI, SAPSII, WBC, hematocrit, hemoglobin, RDW, eGFR, BUN, glucose, sodium, vasopressor, mechanical ventilation, and mannitol.

prognosis of patients (21, 22). For example, in a cross-sectional study from Korea, thiamine intake was found to be critically associated with lower risks of hypertension, myocardial infarction or angina, type 2 diabetes, depression and dyslipidemia after adjusting all potential confounders (23). The provision of thiamine after cardiac arrest improved neurological outcome and 10 days survival in a mouse model (24). In addition, receiving thiamine supplementation was found to have multiple benefits for patients with ventilator-associated pneumonia, including enhancing energy restoration, reducing the likelihood of certain complications, alleviating oxidative stress, and exerting an anti-inflammatory effect (25). These findings hold significant implications for improving patient prognosis and survival rates. Nevertheless, there are few data to support relationship between the thiamine supplementation and in-hospital mortality of TBI patients.

After adjusting multiple confounding factors, our study showed that TBI patients receiving thiamine use have a lower risk of in-hospital mortality, which provided a new perspective to develop therapeutic strategies for TBI. The exact biological mechanisms by which thiamine could exert protective effects for patients with TBI remain unclear. The pivotal role of thiamine in mitochondrial energy metabolism and its involvement in various metabolic processes within mitochondria and peroxisomes *in vivo*, while also conferring cellular resistance against oxidative stress [16, 17]. Mitochondrial dysfunction, oxidative stress and inflammation contribute to the ongoing brain injury and cellular death (7). The administration of thiamine has been demonstrated to mitigate histological brain injury, enhance mitochondrial dynamics, and restore mitochondrial PDH complex activity through activation of the mitochondrial PDH complex (24). Thiamine deficiency has also been proposed as a possible cause of serious damage to brain regions (26). A systematic review suggested that thiamine supplementation may have a positive effect on the delay and prevention of cognitive decline (27). A study conducted on animals demonstrated that thiamine administration can potentially enhance brain homeostatic mechanisms and physiological fitness (28). Previous studies have also described the effect of vitamin for TBI (29, 30). TBI resulted in the manifestation of neurological deficits, accompanied by cerebral edema, disruption of the blood–brain barrier, and an inflammatory response (31). According to the above literature, Thiamine, in its active

form TPP, plays a pivotal role in central nervous system energy metabolism by supporting oxidative decarboxylation reactions critical for ATP production. Additionally, it modulates neurotransmitter synthesis and myelin lipid metabolism, both of which are essential for maintaining neuronal integrity and signal transduction. In addition, our study revealed significant associations between thiamine administration and in-hospital mortality among elderly patients (≥65 years), male individuals, and those with severe TBI. These results also suggest that thiamine supplementation may confer prognostic benefits within this specific population.

However, this study has several limitations. First, due to its nature of single-center retrospective design, selection bias was inevitable. Second, although multivariate adjustment was employed, certain potential confounding factors that could impact the mortality of TBI patients, such as brain imaging data, administration time of thiamine and dosage of thiamine, were unobtainable in this MIMIC-IV database. Finally, this study was solely performed utilized data of patients admitted to the ICU, further investigation is warranted to explore the potential impact of thiamine on the prognosis of TBI patients in general wards.

Conclusion

In short, thiamine administration may reduce in-hospital mortality for patients with TBI admitted to the ICU. Nevertheless, further randomized controlled trials with large sample sizes are needed to confirm the efficacy of thiamine in TBI treatment.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: MIMIC-IV database, https://mimic.physionet.org/iv/.

Ethics statement

The requirement of ethical approval was waived by the Third Affiliated Hospital of Sun Yat-sen University for the studies involving humans. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SG: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. ZZ: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. WZ: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

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.2025.1448439/full#supplementary-material

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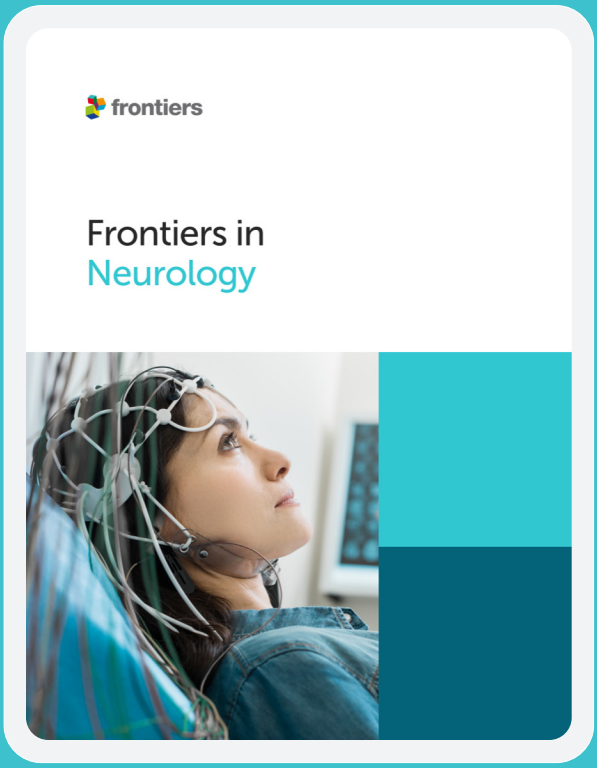

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