



Hyperbaric oxygen therapy (HBOT) for neurocognitive deficits following traumatic brain injury: a systematic review and meta-analysis

Sufyan Shahid, MBBS^a, Humza Saeed, MBBS^b, Masab Ali, MBBS^c, Muhammad Hassan, MBBS^c, Sara Hira, MBBS^d, Musa Kakakhel, MBBS^e, Ayesha Batool, MBBS^f, Abdullah Farooq, MBBS^g, Syeda Noor Us Saba, MBBS^h, Muhammad Husnain Ahmad, MD^{i,*}

Background: Despite traumatic brain injury (TBI) being a leading cause of disability worldwide, it often results in long-term neurocognitive deficits. While conventional treatment options remain limited, hyperbaric oxygen therapy (HBOT) has been proposed as a potential adjunctive intervention due to its ability to enhance oxygen delivery and reduce inflammation. We performed a systematic review and meta-analysis to evaluate the efficacy of HBOT in improving neurocognitive outcomes for TBI patients.

Methods: PubMed, Embase, and Cochrane Central databases were searched for studies on HBOT efficacy in neurocognitive deficits in TBI. Statistical analysis was performed using RevMan v.5.4. A random-effects model was applied to pool mean differences (MDs) and 95% confidence intervals ($P < 0.05$). Risk of Bias 2 (RoB-2) and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tools were used to assess the risk of bias in included randomized controlled trials (RCTs) and non-randomized studies (NRSs), respectively.

Results: Across four studies (250 patients; mean age 25 years, 43% female), HBOT significantly improved multiple neurocognitive domains in TBI patients. The most pronounced improvements were observed in memory (MD 10.13, $P < 0.00001$) and attention (MD 7.99, $P < 0.00001$), with additional benefits in general cognition scores (MD 7.47, $P = 0.003$), executive function (MD 7.16, $P = 0.002$), information processing speed (MD 7.48, $P = 0.01$), and motor skills (MD 5.19, $P < 0.00001$). RCTs had a low risk of bias, while NRSs had a moderate risk of bias due to confounding.

Conclusion: HBOT demonstrates potential in mitigating neurocognitive impairments associated with TBI. Proposed mechanisms underlying its effects include enhanced oxygenation, reduced inflammation and expression of matrix metalloproteinase, decreased brain swelling, and improved outcomes. However, larger trials with standardized protocols are needed to establish the optimal therapeutic role of HBOT in TBI management.

Keywords: hyperbaric oxygen therapy, meta-analysis, neurocognitive deficits, systematic review, traumatic brain injury

^aDepartment of Internal Medicine, Khawaja Muhammad Safdar Medical College, Sialkot, Pakistan, ^bDepartment of Internal Medicine, Rawalpindi Medical University, Rawalpindi, Pakistan, ^cDepartment of Internal Medicine, Punjab Medical College, Faisalabad, Punjab, Pakistan, ^dDepartment of Ophthalmology, FMH College of Medicine and Dentistry, Lahore, Pakistan, ^eDepartment of Medicine, Hayatabad Medical Complex, Peshawar, Pakistan, ^fDepartment of Internal Medicine, Allama Iqbal Medical College, Lahore, Pakistan, ^gDepartment of Internal Medicine, Lahore Medical and Dental College, Lahore, Pakistan, ^hDepartment of Ophthalmology, AlShifa Eye Trust, Kohat, Pakistan and ⁱDepartment of Medicine, Tentshev Satkynbai Memorial Asian Medical Institute, Kant, Kyrgyzstan

All authors contributed to the article and approved the submitted version.

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*Corresponding author. Address: Department of Medicine, Tentshev Satkynbai Memorial Asian Medical Institute, 58 Gagarina, Kant 725012, Kyrgyzstan. E-mail: husnainahmad601@gmail.com (M. H. Ahmad).

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Introduction

Traumatic brain injury (TBI) refers to damage to the brain caused by an external force and is a major global cause of disability and mortality, affecting millions each year^[1]. In the emergency department setting, TBI represents a substantial health and economic burden. Epidemiological data indicate that males experience a 53% higher incidence of TBI and incur nearly twice the health-care costs compared to females^[2]. The neurological impairments resulting from TBI vary depending on the location and severity of the injury. They can significantly reduce survivors' quality of life and functional independence (i.e., the ability to perform daily activities without assistance). Common cognitive deficits include memory loss, attention difficulties, and emotional dysregulation.

Additionally, neuropsychiatric complications—such as mood and anxiety disorders, post-concussive syndrome, personality changes, aggression, and psychosis—are frequently observed after moderate to severe TBI, contributing to long-term morbidity. Regardless of injury severity, attention, memory, and executive functioning disturbances are prevalent. Higher-order cognitive processes, including executive function (which refers to higher-order cognitive skills such as planning, problem-solving, and impulse control), social behavior (“social intelligence,” which refers to the capacity to navigate social interactions appropriately), and motivation, are also commonly affected^[3]. Despite

these widespread impairments, effective therapeutic options for neurocognitive deficits remain limited, highlighting the need to explore novel and promising treatment approaches^[4–6].

Hyperbaric oxygen therapy (HBOT), which involves delivering 100% oxygen at increased atmospheric pressure in a sealed chamber, has emerged as a promising therapeutic approach for TBI. By enhancing oxygen delivery to injured tissues, HBOT may support neuroregeneration and help mitigate the secondary injury cascade associated with TBI^[7]. HBOT also decreases brain swelling, promotes axonal sprouting and synapse remodeling, improves motor function recovery, increases cerebral glucose utilization, and improves neurological outcomes in TBI patients^[8]. Although some studies have suggested positive outcomes, the evidence for the efficacy and safety of HBOT for TBI is still inconclusive and controversial^[9–15].

This systematic review and meta-analysis pooled evidence from studies that assessed the role of HBOT in patients with TBI-related neurocognitive deficits. The objective was to synthesize the available evidence and provide a comprehensive assessment of HBOT's effects on various domains of neurocognition in individuals recovering from TBI.

Methods

This article is compliant with the TITAN guidelines^[16].

We performed this systematic review and meta-analysis to evaluate the efficacy of HBOT in improving neurocognitive outcomes for TBI patients. This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines^[17]. Also, this study has been conducted and reported following the Assessing the Methodological Quality of Systematic Reviews guidelines to ensure methodological consistency and transparency throughout the systematic review process^[18]. The study protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO). The inclusion criteria for the studies were based on the PICO (Patient, Intervention, Comparison, and Outcome) framework, commonly used in systematic reviews and meta-analyses. In this framework, “P” represents patients with TBI, “I” refers to HBOT, “C” refers to pre-HBOT neurocognitive states, and “O” relates to improvement in neurocognitive outcomes after the therapy.

Literature review and search strategy

PubMed, Embase, and Cochrane Central were systematically searched from their inception to November 2024 without any language restrictions to identify relevant articles. The search strategy comprised the following keywords: (TBI OR “traumatic brain injury” OR “post-concussion syndrome” OR PCS) AND (“hyperbaric oxygen therapy” OR HBOT OR “hyperbaric oxygenation” OR “oxygen therapy”). The detailed search strategy is provided in Supplemental Digital Content Table S1, available at: <http://links.lww.com/MS9/A961>.

References of the included articles were also searched to identify additional relevant studies.

HIGHLIGHTS

- Traumatic brain injury (TBI) is a leading cause of disability worldwide, often resulting in long-term neurocognitive deficits with limited effective treatment options.
- This systematic review and meta-analysis evaluated the efficacy of hyperbaric oxygen therapy (HBOT) in improving neurocognitive outcomes for TBI patients. Four studies involving 250 patients (mean age 25 years, 43% female) were analyzed, including both randomized controlled trials and non-randomized studies.
- The findings revealed significant post-HBOT improvements in neurocognitive deficits, including general cognitive scores, memory, attention, executive function, information processing speed, and motor skills.
- HBOT enhances oxygenation, reduces inflammation and matrix metalloproteinase expression, decreases brain swelling, and improves functional outcomes.
- Despite these promising results, larger trials with standardized protocols are necessary to establish the optimal therapeutic role of HBOT in managing TBI.

Eligibility criteria and outcomes

Both randomized controlled trials (RCTs) and non-randomized studies (NRSs) were included if they met the following inclusion criteria: (1) involved patients of TBI of any severity, (2) assessed the efficacy of HBOT using a common assessment tool, i.e., NeuroTrax for this study, and (3) reported one of the outcomes of interest.

The primary outcomes for this review included general cognitive score, memory, attention, executive function, information processing speed (IPS), and motor skills. Cognitive outcomes were assessed via NeuroTrax, with the general cognitive score reflecting composite performance. Domain-specific measures included verbal and non-verbal memory (immediate/delayed recall), attention (sustained, selective, divided), executive function (planning, flexibility, problem-solving), IPS (timed response accuracy), and motor skills (fine motor and psychomotor function).

The abstracts without full-length articles, letters, conference abstracts, animal studies, and studies addressing brain injuries or neurological disorders other than TBI were excluded.

Study selection and data extraction

The search results obtained from the databases were exported to EndNote version 20.5. After removing duplicates, two authors independently reviewed the titles and abstracts to look for potentially eligible articles. The studies were then selected for full-text review, and disagreements were solved with the help of a third reviewer. The data extracted includes the author's name, year of publication, number of participants, study design, time since trauma, severity of trauma, dosage and duration of HBOT, and number of daily HBOT sessions. For crossover trials, data were collected for treatment and control periods separately.

Statistical and subgroup analysis

Meta-analyses were conducted using Review Manager (RevMan) version 5.4 to pool mean differences (MDs) with

95% confidence intervals (CIs) with statistically significant defined as $P < 0.05$. The Cochran Q test and I^2 statistics were used to assess heterogeneity; P values < 0.05 and $I^2 > 50\%$ were considered significant for heterogeneity^[19]. The DerSimonian and Laird Random effects model was applied for all outcomes^[20]. A subgroup analysis was performed to determine the impact of different study variables on the effect sizes observed. Meta-regression assessed the relationship between patients' age and MDs observed for outcomes^[21].

Quality assessment

Two authors independently assessed the quality of included studies. Revised Cochrane risk of bias (RoB-2)^[22] and ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions)^[23] were used to assess the quality of RCTs and NRSs, respectively. Studies were scored as low risk of bias, high risk of bias, or some concerns depending on their selection, performance, detection, attrition, and reporting biases. Any disagreements were resolved by consensus. Publication bias assessment was impossible due to the limited number of studies (<10).

Results

Study selection

A comprehensive literature search yielded 1291 studies from three databases: PubMed, Embase, and Cochrane Central. After removing duplicate and ineligible records, 171 studies were left for eligibility assessment. Ultimately, full-text review identified four studies that fulfilled the inclusion criteria and were included in the final analysis.^[21–24] The detailed results of study screening are provided in the PRISMA flow diagram (Fig. 1).

Study characteristics

This systematic review and meta-analysis included four studies, two of which were trials^[21,22] and two were retrospective cohort studies^[23,24]. The included studies involved 250 patients; mean ages ranged from 11.6 to 44 years, with 57% of participants (142 of 250) identified as males. Participants received 40–60 HBOT sessions, with individual sessions lasting between 60 and 90 min, depending on the study protocol. About 60%

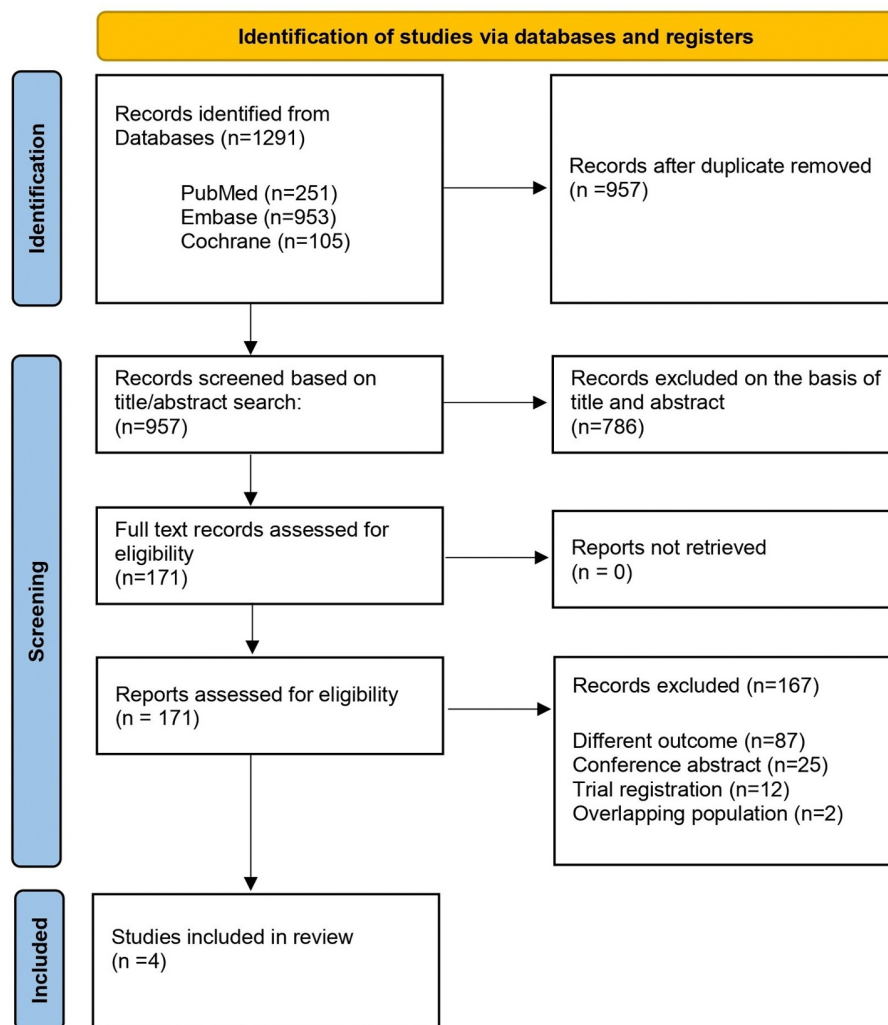


Figure 1. PRISMA flow diagram of the included studies.

(151 of 250) of the patients suffered mild TBI. The detailed characteristics of the included studies are shown in Table 1.

Quality assessment

Both of the RCTs included were rated as low risk of bias.^[24,25] The two retrospective studies were classified as having moderate risk of bias, mainly due to confounding^[26] and bias in the selection of reported results^[26,27]. The results of quality assessment are given in Supplemental Digital Content Figure S1A, B, available at: <http://links.lww.com/MS9/A961>.

Outcomes

TBI patients receiving HBOT showed a statistically significant improvement in scores of all the neurocognitive outcomes assessed by NeuroTrax. The greatest MD was observed in the outcome of memory (MD 10.13; 95% CI 7.40–12.86), whereas the lowest MD was in the outcome of motor skills (MD 5.19; 95% CI 3.00–7.37) of the patients. Similarly, other outcomes including attention (MD 7.99; 95% CI 6.06–9.92), executive function (MD 7.16; 95% CI 2.70–11.62), general cognitive scores (MD 7.47; 95% CI 2.52–12.41), and IPS (MD 7.48; 95% CI 1.65 to 13.31) were also significantly improved post-HBOT. The detailed results of all outcomes are shown in Figure 2A–E.

Subgroup analysis

The subgroup analysis was performed to determine the impact of study design on the effect sizes and corresponding heterogeneity observed in the results. After studies were stratified according to study design, i.e., trials and NRs, the results were as follows:

- Memory: A greater improvement in memory was reported by the trials (MD 12.909; 95% CI 5.220–20.598, $P < 0.001$) as compared to NRs (MD 9.727; 95% CI 6.806–12.648, $P < 0.001$).
- Attention: Similarly, attention was also significantly better in patients in the trial group (MD 8.90; 95% CI 2.68–15.108, $P = 0.005$) than in NRs (MD 7.894; 95% CI 5.861–9.928, $P < 0.001$).
- Executive function: Patients in the trial subgroup demonstrated lesser improvement in executive function (MD 4.261; 95% CI –5.120–13.642, $P = 0.373$) as compared to those in the NRs (MD 8.742; 95% CI 3.458–14.207, $P = 0.001$).
- IPS: A lesser improvement in IPS was reported by the trials (MD 5.203; 95% CI –4.126–14.532, $P = 0.274$) than NRs (MD 9.109; 95% CI 1.076–17.142, $P = 0.026$).

Subgroup analysis for the other two outcomes including general cognitive score and motor skills could not be performed due to unavailability of enough studies (≥ 2) to make a subgroup. Forest plots representing the results of subgroup analysis are given in Supplemental Digital Content Figure S2A–D, available at: <http://links.lww.com/MS9/A961>.

Meta regression

Out of four studies included in the analysis, one had patients with a mean age of < 18 years, and the other three had a mean age > 18 years. Therefore, meta-regression was performed to assess

the relationship between the age of patients and MDs observed for outcomes. The results showed a significant positive association between the age of patients and the MD in scores of all neurocognitive outcomes except memory. This means that the greater the TBI patient's age, the greater the efficacy of HBOT in improving neurocognitive deficits present. The regression plots representing these associations are shown in Supplemental Digital Content Figure S3A–D, available at: <http://links.lww.com/MS9/A961>.

Discussion

This systematic review and meta-analysis offers a focused synthesis of the neurocognitive effects of HBOT in TBI, addressing a critical evidence gap in the literature where cognitive outcomes have been underreported or inconsistently assessed. It delineates the therapeutic scope of HBOT across specific cognitive domains, informing translational research and clinical neurorehabilitation strategies.

It suggests that HBOT may offer neurocognitive benefits in patients with TBI, particularly in domains such as memory, attention, and general cognitive function. However, these findings must be interpreted in light of the methodological variability and the limited number of studies available.

All the included studies employed a similar computerized assessment technique, i.e., NeuroTrax, to assess the cognitive function of patients both before and after treatment with HBOT^[24–27].

Previous studies suggest that HBOT improves cognitive outcomes by increasing angiogenesis and the oxygen supply to the damaged areas of the brain for better repair^[28–31] and neuronal regeneration^[32,33]. In addition, by enhancing the mitochondrial function, HBOT may boost levels of neurotrophins and nitric oxide and improve cellular metabolism in both neurons and glial cells^[31]. A previous review article by Andrews *et al* discussed the efficacy of HBOT in treating patients with posttraumatic stress disorder (PTSD)^[34]. It included military trials, case reports and case series and showed that HBOT significantly improved the symptoms of PTSD^[35–37]. The potential adverse effects of HBOT identified in this review included barotrauma, exacerbation of anxiety, headache, nausea, sinus squeeze, vision change, somnolence, and hyperventilation^[9,11,35,36,38,39]. Late complications may be due to oxidative stress^[9].

Of the four included studies in our analysis, two RCTs compared outcomes in patients receiving HBOT with those receiving sham control treatment. In the treated group, the outcomes of memory and general cognitive score were significantly improved, while the results of the other four outcomes differed between the studies^[24,25]. In the Hadanny 2022 trial, the outcomes of attention, IPS, motor skills, and executive function were not significantly improved ($P > 0.05$). This may be influenced by the difficult outcome measurements due to the presence of children in this trial^[25].

The retrospective observational studies included in the meta-analysis also showed a significant improvement in all the cognitive outcomes of patients post-treatment^[26,27]. These studies have their strengths, such as being carried out at a later stage of the disease, and also on civilian populations that did not have any potential secondary gain (such as financial compensation) by reporting sick.

Table 1 Characteristics and summary of the studies included in the review															
Author	Study design	No. of patients	M/F ratio	Mean age	Daily number of HBOT sessions	Dosage and duration of HBOT	Control	Time since trauma (years)				Severity of trauma			
								HBOT	Control	Mild		Moderate		Severe	
										HBOT	Control	HBOT	Control	HBOT	Control
Hadanny 2022	RCT	25	4:1	11.6 ± 2.32 years	60	5 days/week, 60 min per session, 100% oxygen at 1.5 ATA	Sham treatment	4.89 ± 2.23	4.85 ± 1.78	11 (73.3)	7 (70.0)	2 (13.3)	3 (30.0)	2 (13.3)	0 (0.0)
Boussi-gross 2013	RCT	56	43:57	44 years	40	5 days/week, 60 min per session, 100% oxygen at 1.5 ATA	Crossover approach: 2-month control period of no treatment, followed by a subsequent 2-month period of 40 HBOT sessions	2.88 ± 1.4	2.64 ± 1.3	32 (100%)	24 (100%)	NA	NA	NA	NA
Hadanny 2018	Retrospective analysis	154	58:42	42.7 ± 14.6 years	52.0 ± 9.9	5 days/week, 60/90 min per session, 100% at 1.5/2 ATA	NA	4.6 ± 5.8	NA	69 (44.8%)	NA	24 (15.6%)	NA	61 (39.6%)	NA
Tal 2017	Retrospective analysis	15	53:47	35.8 ± 3.5 years	60	5 days/week, 90 min per session, 100% oxygen at 2 ATA	NA	6.7 ± 2.1	NA	8 (53.3%)	NA	2 (13.3%)	NA	5 (33.4%)	NA

HBOT: hyperbaric oxygen therapy; ATA: atmospheres absolute; NA: not applicable.

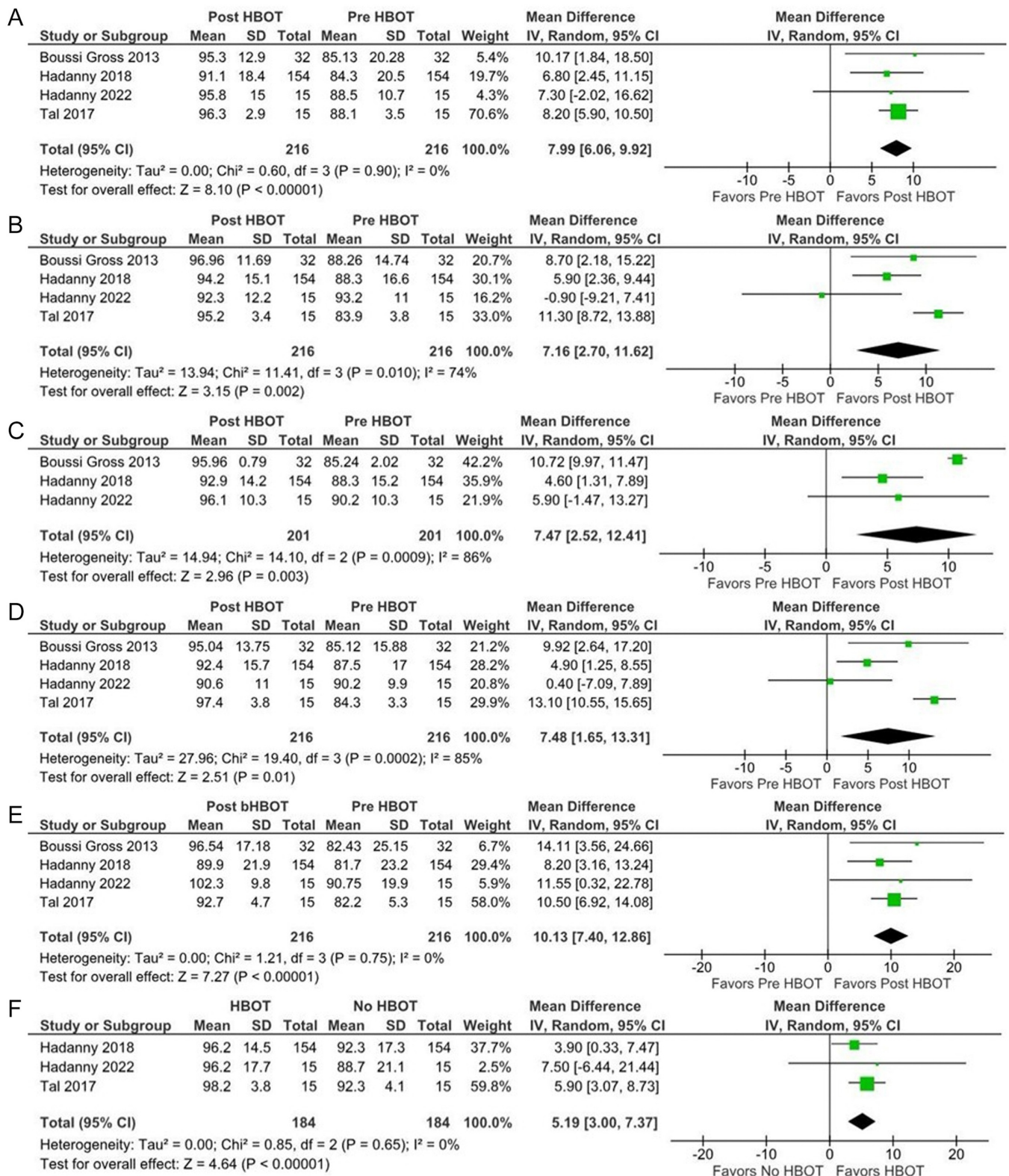


Figure 2. (A) Forest plot for the outcome of attention comparing the mean difference between pre-HBOT and post-HBOT scores. (B) Forest plot for the outcome of executive function comparing the mean difference between pre-HBOT and post-HBOT scores. (C) Forest plot for the outcome of the general cognitive score comparing the mean difference between pre-HBOT and post-HBOT scores. (D) Forest plot for the outcome of information processing speed (IPS) comparing the mean difference between pre-HBOT and post-HBOT scores. (E) Forest plot for the outcome of memory comparing the mean difference between pre-HBOT and post-HBOT scores. (F) Forest plot for the outcome of motor skills comparing the mean difference between pre-HBOT and post-HBOT scores.

Hadanny 2018 had the largest cohort of patients in which the cognitive efficacy of HBOT was seen^[27].

In Tal 2017, however, the outcome of attention was not significantly improved ($P = 0.062$)^[26].

Among the included studies, the General cognitive score, IPS, and executive function outcomes gave heterogeneous results in the pooled analysis, mainly due to the heterogeneity in the ages of patients among the studies, as clear by the pediatric population in one of the RCTs^[25]. The mean time to injury and HBOT protocols also varied among the studies, which may have contributed to the heterogeneity in the pooled analysis results.

The larger effect sizes observed in NRSs relative to RCTs, particularly for executive function and IPS, likely reflect inherent biases in observational designs, such as unmeasured confounding and selection bias. In contrast, RCTs provide more conservative, methodologically rigorous estimates. These findings underscore the importance of carefully interpreting pooled results and considering the inherent differences in study design when evaluating clinical outcomes. The larger effect sizes in NRSs do not invalidate the findings but rather highlight the need for more rigorous trials to confirm the observed benefits of HBOT in cognitive rehabilitation following TBI.

To substantiate and expand upon these findings, future research must adopt rigorous methodological standards, including:

- Larger, multicenter RCTs with stratification by age, injury severity, and chronicity.
- Standardized HBOT protocols (pressure, duration, and number of sessions).
- Uniform cognitive outcome measures, possibly extending beyond NeuroTrax to include ecologically valid and functionally predictive tests.
- Mechanistic studies integrating imaging and biomarker endpoints to validate the neurobiological underpinnings of HBOT efficacy.
- Exploration of dose–response relationships and identification of potential therapeutic windows post-injury.

Such investigations should also consider long-term follow-up to assess the durability of cognitive gains and potential delayed adverse effects such as oxidative stress–induced injury.

Although still exploratory, the findings of this meta-analysis suggest that HBOT could become a viable adjunct in the cognitive rehabilitation of TBI patients. Should future high-quality trials confirm these benefits, the implications for clinical guidelines, rehabilitation protocols, and potentially military and civilian health systems are substantial. Policymakers and healthcare providers must also consider the cost-effectiveness and logistical feasibility of HBOT in various healthcare settings. Integration into treatment pathways would require clear criteria for patient selection and monitoring and standardized safety protocols to mitigate known risks such as barotrauma and oxidative injury.

Limitations

To our knowledge, this is the first and largest up-to-date systematic review and meta-analysis focusing on the efficacy of HBOT for neurocognitive deficits in patients with TBI.

However, it has several limitations: (1) Two of the included studies are observational retrospective analyses with moderate risk of bias, as the influence of residual confounders could not be completely excluded. (2) In the other two randomized control trials, pre-HBOT and post-HBOT values are given instead of the standard sham control originally designed by the studies. The study samples of three out of four studies were relatively limited and underpowered due to the patients' hesitance to be included. (3) Significant heterogeneity and inconsistent findings were noted in executive function and IPS. This may be due to the heterogeneity in the ages of patients among the studies, as clear by the pediatric population in one of the RCTs. (4) We only have four studies with a total of 250 participants, which might limit the generalizability of the findings. (5) Only studies using the NeuroTrax tool were included to ensure consistency in outcome measurement; this may have excluded other potentially relevant studies using alternative, validated cognitive scales, which might introduce selection bias. (6) Given the limited number of studies (<10), formal assessment of publication bias was not statistically justified. Nonetheless, the consistent directionality of positive findings may reflect underlying reporting or publication bias, a known issue in HBOT literature. This is a methodological limitation, and results should be interpreted accordingly. (7) Given the limited number of studies, methodological variability, and outcome measures heterogeneity, this review should be considered exploratory. (8) Gray literature databases such as ProQuest were not systematically searched, which may have led to the exclusion of relevant unpublished or non-peer-reviewed studies. (9) The impact of the time interval between TBI and HBOT initiation could not be assessed due to inconsistent reporting across studies.

More RCTs employing HBOT as an intervention and a predefined control group are therefore needed to evaluate further the cognitive efficacy in patients with TBI. Some major reasons for the lack of adequate RCTs include (1) adverse effects of barotrauma, (2) ethical and logistic issues associated with sham control, and (3) hesitancy of patients to consent to inclusion in these trials. Poor patient compliance may also be another factor in the non-availability of adequate RCTs on this topic. Therefore, RCTs with an optimal ethical and logistic protocol for the sham control group, an optimal sample size, and appropriate follow-up duration are needed.

Conclusion

Hyperbaric oxygen treatment improves cognitive function in patients with TBI, regardless of the age of the patients and the severity of trauma. However, due to the smaller number of studies available and significant heterogeneity, the conclusions drawn from this meta-analysis should be viewed as exploratory. Future randomized trials are needed to strengthen the evidence in this regard further.

Ethical approval

Ethical approval is not required for this systematic review.

Consent

Informed consent was not required for this systematic review.

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Author contributions

S.S. is responsible for conceptualization and, along with H. S. and M.H.A., wrote the main manuscript text. A.B. and A. F. prepared figures. S.N.U.S., M.A., and M.K. prepared tables. M.A., M.H., and S.H. reviewed and edited the final draft. All authors reviewed the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

The study protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42024500393.

Guarantor

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Data availability statement

All the datasets generated during and/or analyzed during the current study are publicly available.

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Presentation

None.

AI use declaration

No generative artificial intelligence (AI) tools were used in the research, data analysis, or manuscript writing.

References

- [1] Dewan MC, Rattani A, Gupta S, *et al.* Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2019;130:1080–97.
- [2] Fu TS, Jing R, McFaull SR, *et al.* Health & economic burden of traumatic brain injury in the emergency department. *Can J Neurol Sci* 2016;43:238–47.
- [3] Arciniegas DB, Held K, Wagner P. Cognitive impairment following traumatic brain injury. *Curr Treat Options Neurol* 2002;4:43–57.
- [4] Freire MAM, Rocha GS, Bittencourt LO, *et al.* Cellular and molecular pathophysiology of traumatic brain injury: what have we learned so far? *Biology (Basel)* 2023;12:1139.
- [5] Reilly PL, Graham DI, Adams JH, *et al.* Patients with head injury who talk and die. *Lancet* 1975;2:375–77.
- [6] Bayir H, Clark RSB, Kochanek PM. Traumatic brain injury in infants and children: mechanisms of secondary damage and treatment in the intensive care unit. *Crit Care Clin* 2003;19:529–49.
- [7] Hampson NB, editor. *Hyperbaric Oxygen Therapy: 1999 Committee Report*. Kensington, MD: Undersea and Hyperbaric Medical Society; 1999.
- [8] Hu Q, Manaenko A, Xu T, *et al.* Hyperbaric oxygen therapy for traumatic brain injury: bench-to-bedside. *Med Gas Res* 2016;6: 102–10.
- [9] Harch PG, Andrews SR, Rowe CJ, *et al.* Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial. *Med Gas Res* 2020;10:8–20.
- [10] Harch PG, Fogarty EF, Staab PK, *et al.* Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post-traumatic stress disorder: a case report. *Cases J* 2009;2:6538.
- [11] Shytle RD, Eve DJ, Kim SH, *et al.* Retrospective case series of traumatic brain injury and post-traumatic stress disorder treated with hyperbaric oxygen therapy. *Cell Transplant* 2019;28:885–92.
- [12] Harch PG. Hyperbaric oxygen therapy for post-concussion syndrome: contradictory conclusions from a study mischaracterized as sham-controlled. *J Neurotrauma* 2013;30:1995–99.
- [13] Hu Q, Manaenko A, Guo Z, *et al.* Hyperbaric oxygen therapy for post concussion symptoms: issues may affect the results. *Med Gas Res* 2015;5:10.
- [14] Alashram AR, Padua E, Romagnoli C, *et al.* Hyperbaric oxygen therapy for cognitive impairments in patients with traumatic brain injury: a systematic review. *Appl Neuropsychol Adult* 2023;30:602–13.
- [15] Wang F, Wang Y, Sun T, *et al.* Hyperbaric oxygen therapy for the treatment of traumatic brain injury: a meta-analysis. *Neurol Sci* 2016;37:693–701.
- [16] Agha RA, Mathew G, Rashid R, *et al.* Transparency in the reporting of Artificial INtelligence - the TITAN guideline. *Prem J Sci* 2025;10:100082.
- [17] Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [18] Shea BJ, Reeves BC, Wells G, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
- [19] Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- [20] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- [21] Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21:1559–73.
- [22] Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomized trials. *BMJ* 2019;366:14898.
- [23] Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016;355: i4919.
- [24] Boussi-Gross R, Golan H, Fishlev G, *et al.* Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury – randomized prospective trial. *PLoS ONE* 2013;8:e79995.
- [25] Hadanny A, Catalogna M, Yaniv S, *et al.* Hyperbaric oxygen therapy in children with post-concussion syndrome improves cognitive and behavioral function: a randomized controlled trial. *Sci Rep* 2022;12: 15233.
- [26] Tal S, Hadanny A, Sasson E, *et al.* Hyperbaric oxygen therapy can induce angiogenesis and regeneration of nerve fibers in traumatic brain injury patients. *Front Hum Neurosci* 2017;11:508.
- [27] Hadanny A, Abbott S, Suzin G, *et al.* Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis. *BMJ Open* 2018;8:e023387.
- [28] Harch PG, Andrews SR, Fogarty EF, *et al.* A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. *J Neurotrauma* 2012;29:168–85.
- [29] Neubauer RA, James P. Cerebral oxygenation and the recoverable brain. *Neurol Res* 1998;20:S33–6.
- [30] Golden ZL, Neubauer R, Golden CJ, *et al.* Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy. *Int J Neurosci* 2002;112:119–31.

- [31] Zhang JH, Lo T, Mychaskiw G, *et al.* Mechanisms of hyperbaric oxygen and neuroprotection in stroke. *Pathophysiology* 2005;12:63–77.
- [32] Kuffler DP. The role of hyperbaric oxygen therapy in enhancing the rate of wound healing with a focus on axon regeneration. *P R Health Sci J* 2011;30:35–42.
- [33] Neubauer RA, Walker M. *Hyperbaric Oxygen Therapy*. Garden City Park, NY: Avery Publishing Group; 2000.
- [34] Harch PG. “systematic review and dosage analysis: hyperbaric oxygen therapy efficacy in mild traumatic brain injury persistent postconcussion syndrome”. *Front Neurol* 2022;13:815056.
- [35] Miller RS, Weaver LK, Bahraini N, *et al.* HOPPS trial team. effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. *JAMA Intern Med* 2015;175:43–52.
- [36] Weaver LK, Wilson SH, Lindblad AS, *et al.* Hyperbaric oxygen for post-concussive symptoms in United States military service members: a randomized clinical trial. *Undersea Hyperb Med* 2018;45:129–56.
- [37] DeGraba TJ, Williams K, Koffman R, *et al.* Efficacy of an interdisciplinary intensive outpatient program in treating combat-related traumatic brain injury and psychological health conditions. *Front Neurol* 2021;11:580182.
- [38] Harch PG, Andrews SR, Fogarty EF, *et al.* Case control study: hyperbaric oxygen treatment of mild traumatic brain injury persistent post-concussion syndrome and post-traumatic stress disorder. *Med Gas Res* 2017;7:156–74.
- [39] Wolf EG, Prye J, Michaelson R, *et al.* Hyperbaric side effects in a traumatic brain injury randomized clinical trial. *Undersea Hyperb Med* 2012;39:1075–82.