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Research Article

Hyperbaric oxygen for moderate-to-severe traumatic brain injury: outcomes 5–8 years after injury

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Abstract

The use of hyperbaric oxygen (HBO_2) in the field of traumatic brain injury (TBI) is becoming more widespread and increasing yearly, however there are few prognostic reports on long-term functional efficacy. The aim of this study was to assess the functional prognosis of patients with moderate-to-severe TBI 5–8 years following HBO_2 treatments and to explore the optimal HBO_2 regimen associated with prognosis, using a retrospective study. Clinical data were retrospectively collected as a baseline for patients with moderate-to-severe TBI treated with HBO_2 during inpatient rehabilitation from January 2014 to December 2017. The primary outcome measure was the Disability Rating Scale (DRS) and the secondary outcome measure was the Glasgow Outcome Scale. A total of 133 patients enrolled, with 9 (6.8%) dying, 41 (30.8%) remaining moderately disabled or worse (DRS scores 4–29), 83 (62.4%) remaining partially/mildly disabled or no disability (DRS scores 0–3). Logistic regression analysis revealed that age at injury (odds ratio (OR), 0.96; 95% confidence interval (CI), 0.92–0.99), length of intensive care unit stay (OR, 0.94; 95% CI, 0.88–0.99), and HBO_2 sessions (OR, 0.97; 95% CI, 0.95–0.99) were variables that independently influenced long-term prognosis. Cubic fitting models revealed that 14 and 21.6 sessions of HBO_2 could be effective for moderate and severe TBI, respectively. This study highlighted that HBO_2 in moderate-to-severe TBI may contribute to minimize death and reduce overall disability in the long-term. However, clinicians should be cautious of the potential risk of adverse long-term prognosis from excessive HBO_2 exposure when tailoring individualized HBO_2 regimens for patients with moderate-to-severe TBI. The study was registered on ClinicalTrials.gov (NCT05387018) on March 31, 2022.

Key Words: disability rating scale; disability; excessive hyperbaric oxygen exposure; follow-up; Glasgow coma scale; hyperbaric oxygen; long-term outcome; regimen; traumatic brain injury

Introduction

Survivors of moderate-to-severe traumatic brain injury (TBI) are frequently left with an array of sequelae, including persistent vegetative state, cognitive impairment, mental disorders, personality changes, physically dysfunction, and so on, which may result in persistent disability and prolonged reliance on others.[1-9]

Hyperbaric oxygen (HBO_2) therapy is the therapeutic administration of 100% oxygen at atmospheric pressures greater than 1 atmosphere absolute. By reducing intracranial pressure, cerebral edema, neuroinflammation, neuronal apoptosis, and increasing cerebral oxygen supply and cerebral glucose utilization, HBO_2 may improve consciousness, cognition, and overall prognosis of patients with TBI.[10-16] Although numerous studies have been published on the use of HBO_2 in TBI,[16-24] there is still some controversy concerning its efficacy, mostly for the following reasons: (1) the underlying therapeutic mechanism has yet to be fully elucidated; (2) HBO_2 has several contraindications, including cerebrospinal fluid leakage and active hemorrhage; and (3) there are a few rare but mild adverse effects, including barotrauma and cerebral and pulmonary oxygen toxicity, when using HBO_2 in TBI.[22,25,26] Furthermore, there were concerns that HBO_2 would just reduce TBI-related mortality while increasing the fraction of survivors in a vegetative state or with severe disability.[27]

To date, the vast majority of clinical HBO_2 trials in TBI have not exceeded a 6-month follow-up,[16,18,21,23] except for one study that extended follow-up to 36 months post-treatment.[24] What is beneficial in the short term may be detrimental in the long term due to the timing of the biochemical and inflammatory effects of brain injury, and vice versa. Long-term follow-up studies for this population are scarce and need to be further elucidated. A number of animal research[10-14,19,20] and clinical study[18] have demonstrated that very early HBO_2 intervention improves the functional prognosis of patients with TBI; however, other studies have found that HBO_2 could provide therapeutic advantages up to 6 months or even years after TBI.[17,28] The potential HBO_2 therapeutic time window for moderate-to-severe TBI has not yet been widely

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established, necessitating further investigation. In addition, multiple hyperbaric treatments have been demonstrated in prior clinical reports to significantly reduce secondary brain injury; however, the total number of sessions varies greatly, ranging from 3 to 120, with the majority of trials utilizing 20–40 sessions.[15-18,21,23,26,29,30] This underscores the need for additional clarification on this therapeutic parameter to figure out the optimal sessions for long-term functional recovery in moderate-to-severe TBI.

This study included patients with moderate-to-severe TBI who started HBO_2 during inpatient rehabilitation within 90 days of the injury. Our objectives were to: (1) determine the functional recovery of moderate-to-severe TBI patients treated with HBO_2 at 5–8 years post-injury; (2) explore the optimal HBO_2 regimen for long-term functional recovery in moderate-to-severe TBI patients based on the time of initiation and the number of sessions of HBO_2 intervention. Based on our previous clinical experience, we hypothesized that HBO_2 would reduce long-term mortality and disability in patients with TBI, and that the earlier the hyperbaric intervention after TBI, the better the prognosis would be; however, the total number of hyperbaric sessions may not necessarily be proportional to the prognosis.

Subjects and Methods

This was a retrospective study conducted by the Second Affiliated Hospital of Zhejiang University School of Medicine and the First People's Hospital of Wenling in China. The Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine approved the project on March 14, 2022 (approval No. 0166). All study protocols were undertaken in line with the *Declaration of Helsinki*. Informed consent of the participants or their chosen legal representatives had been obtained verbally or in writing. The study was registered on ClinicalTrials.gov (NCT05387018) on March 31, 2022.

Subjects

Patients with moderate-to-severe TBI who underwent HBO_2 and neurorehabilitation during inpatient rehabilitation from January 2014 to December 2017 were retrospectively screened. The inclusion criteria were as follows: (1) age range of 18 to 60 years at the time of injury; (2) Glasgow Coma Scale (GCS)[1] score < 13 on emergency admission or GCS score ≥ 13 in emergency department but fell to less than 13 within 48 hours after injury[31]; and (3) HBO_2 treatment within 90 days after injury. The exclusion criteria were as follows: pre-morbid cognitive and/or psychiatric disorders, pregnancy, and history of severe coagulopathy, severe multiple organ failure, penetrating brain damage, intracranial diseases, and spinal cord injury. There were no racial/ethnic or gender-based distinctions.

In principle, HBO_2 treatment would not be offered to TBI-related patients unless their medical condition matched the following criteria: (1) oxygen saturation maintained above 95%; (2) vital signs: temperature 36.5–38.0°C, heart rate 50–100 beats/min, systolic blood pressure 90–150 mmHg and diastolic blood pressure 60–90 mmHg, respiratory rate 12–20 breaths/min; and (3) exclusion of contraindications, such as intracranial or extracranial active bleeding.

One session of hyperbaric chamber (Yantai Moon Oxygen Chamber Co., Ltd., Yantai, Shandong, China) exposure each day, five days per week, lasted ninety minutes, involving compression to intervention pressure (2.0 atmosphere absolute inhaling 100% oxygen) and decompression. In the meantime, physical, cognitive, occupational, swallowing, and speech therapy were provided to each patient based on their specific needs.

Outcome measures

The primary outcome measure was the Disability Rating Scale (DRS), which was designed to track TBI individual's global functional changes. The scale encompasses four domains: employability (inability to work, potential for competitive or sheltered-workshop employment), overall functional level (dependence on others, assistance/supervision, or living independently), and consciousness (eye, motor, and verbal); cognitive capability (feed, toilet, and groom oneself).[32] The total DRS score ranges from 0 (no disability) to 30 (death) and is generally categorized into six categories: dead (scores 30), extreme vegetative state/vegetative state (scores 22–29), extremely severe/severe disability (scores 12–21), moderately severe/moderate disability (scores 4–11), partial/mild disability (scores 1–3) and none (score 0).[2] Based on the DRS score and classification criteria provided above, the outcome of this study was dichotomized as favorable (DRS scores 0–3) or unfavorable (DRS scores 4–30). Patients with a favorable outcome included those who lived independently and were even capable of being employed, but may need assistance with activities; patients with an unfavorable outcome included those who were dependent on others for daily assistance due to cognitive, psychosocial, and/or physical disabilities, as well as those who died.

The secondary outcome measure was the Glasgow Outcome Scale, which is widely used to assess the long-term prognosis of TBI[3,33]: 1 = death, 2 = vegetative state (minimally responsive), 3 = severe disability (conscious but severely disabled and dependent on others for daily assistance), 4 = moderate disability (disabled but independent and able to work in sheltered setting), and 5 = good recovery (resume normal life despite minor deficits).[34]

Procedures

Individuals who met the inclusion and exclusion criteria were screened initially, and detailed medical records were collected and recorded retrospectively as a baseline, including demographic information at the time of injury (date of birth, sex [sex assigned at birth], education, employment, and history of alcohol use), injury characteristics (cause of injury and initial GCS score), and clinical interventions (tracheotomy and/or neurosurgical interventions maneuvers, length of stay in the intensive care unit, and HBO_2 regimens). The GCS verbal domain score for tracheally intubated patients was 1. Between June 2022 and January 2023, two qualified neurorehabilitation physicians used the Glasgow Outcome Scale[33] and the DRS questionnaires[35] to conduct outcome

assessments via telephone or online communication platforms such as WeChat. If patients were functionally impaired and unable to provide reliable information, data were collected from familiar caregivers or close family members.

Statistical analysis

Data were analyzed using the statistical software R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 26 (IBM Corp, Armonk, NY, USA). Descriptive statistics were performed using quartiles for non-normal distribution and counts (percentages) for categorical variables. The mean and standard deviation were calculated for normally distributed continuous data. The results were categorized as favorable (DRS scores 0–3) and unfavorable (DRS scores 4–30). For categorical variables, chi-square and Fisher's exact tests were used to assess differences in demographics, injury characteristics, and clinical interventions between the favorable and unfavorable groups for moderate-to-severe TBI.

Univariate and multivariate analyses were performed using logistic regression. The dependent variables were favorable (DRS scores 0–3) and unfavorable (DRS scores 4–30) outcomes, while the independent variables were age, sex, education level, employment status before injury, drinking history, injury cause, GCS score, tracheotomy, neurosurgical interventions, length of ICU stay, HBO_2 sessions, and HBO_2 initiation time. All variables that were significant in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. The dependent (outcome) variable coding scheme was 0 = unfavorable and 1 = favorable. An odds ratio greater than 1 indicated a higher probability of obtaining a favorable outcome compared to the control group. In addition, a continuous fractional polynomial regression model was used to estimate the trend between hyperbaric variables and DRS scores over time. All reported *P*-values less than 0.05 were deemed statistically significant.

Results

Participants and acute-injury characteristics

A total of 145 patients with moderate-to-severe TBI were enrolled in the study, of whom 12 withdrew during follow-up, leaving 133 eligible for analysis, including 94 (70.7%) males and 39 (29.3%) females. The median [interquartile range (IQR)] age of these patients at the time of injury was 49 (39.5–56.5) years, and the mean GCS score was 7.18 ± 2.16. As shown in **Table 1**, traffic accidents were the main cause (53.4%) followed by falls (39.8%) and others. Only 36 (27.1%) of the patients had more than 9 years of education and 127 (95.5%) of the patients were employed before the injury. Of the 133 patients, 19 (14.3%) had a history of alcohol consumption for more than 10 years, 108 (81.2%) required intensive care on admission with a median (IQR) stay in the intensive care unit of 6 (3, 6) days, 40 (30%) underwent a tracheotomy, and 83 (62.4%) required neurosurgical interventions following injury.

Table 1 shows that compared to patients with a favorable outcome (DRS scores 0–3), patients with an unfavorable outcome (DRS scores 4–30) had lower initial GCS scores (6.54 ± 2.17, $P = 0.0083$), a longer mean intensive care unit stay (median [IQR], 11 [6, 16.75] days, $P < 0.05$), an older median [IQR] age (52 [44–58] years, $P = 0.034$) at the time of injury, more mean HBO_2 sessions (32.5 ± 24.5, $P = 0.002$), and a later mean HBO_2 initiation time (31.7 ± 14.9 days, $P = 0.030$). Those who had undergone tracheotomy were more likely to have a poor outcome ($P = 0.053$). Nevertheless, there was no significant correlation between the long-term prognosis (5–8 years) of moderate-to-severe TBI and factors such as sex, educational level, employment status, history of alcohol abuse, cause of injury, or neurosurgical procedures. The comparison of co-morbidities (e.g., hypertension, diabetes mellitus, atrial fibrillation, etc.) and concomitant injuries (thoracic, limb, spinal, and pelvic injuries) between the favorable and unfavorable groups also revealed no statistically significant differences (**Additional Table 1**).

Outcomes between moderate and severe TBI

Approximately two-thirds (62.4%) of the 133 patients had a favorable outcome (DRS scores 0–3), of which 42 (31.6%) were partially or mildly disabled (DRS score 1–3) and 41 (30.8%) fully regained their pre-injury function (DRS score 0). Of the 133 patients, 41 (30.8%) were moderately disabled or worse (DRS score 4–29). Nine patients (9/133) died within 3–24 months of their injury, resulting in a 6.8% mortality rate (**Figure 1**). Patients living independently but with persistent moderate or mild disability (Glasgow Outcome Scale scores 4–5) accounted for 110 (82.7%) of the total group (**Table 2**).

As shown in **Table 2** and **Figure 2**, all patients were subsequently categorized into two subgroups: severe TBI (GCS scores 3–8) and moderate TBI (GCS scores 9–12). Approximately three-quarters of the patients had severe TBI based on the initial GCS score and their mortality rate was more than twice as high as that of patients with moderate TBI [7.8% (8/102) *vs*. 3.2% (1/31)]. 60.8% (62/102) of the patients with severe TBI had a favorable outcome (DRS scores 0–3) and 6.9% (7/102) remained severely disabled or in a vegetative state (DRS scores 12–29) 5–8 years post-injury. Nonetheless, of the 31 patients with moderate TBI, 21 (67.7%) had a favorable outcome (DRS scores 0–3), one patient died, and none were in a vegetative state or had residual severe disability (DRS scores 12–29).

Analysis of potential risk factors

As shown in **Table 3**, univariate analysis revealed that age, GCS score, length of intensive care unit stay, HBO_2 sessions, and HBO_2 initiation timing (all $P < 0.05$) differed significantly between subgroups. The parameters of age (odds ratio (OR), 0.96; 95% confidence interval (CI), 0.92–0.99; $P = 0.031$), length of intensive care unit stay (OR, 0.94; 95% CI, 0.88–0.99; $P = 0.034$), and HBO_2 sessions (OR, 0.97; 95% CI, 0.95–0.99; $P = 0.005$) were found to be the independent factors associated with favorable outcomes for moderate-to-severe TBI patients 5–8 years after injury (**Table 3**).

Relationships between HBO_2 regimen and long-term prognosis

A cubic fitting model based on the correlation between DRS scores and the number of HBO_2 sessions is shown in **Figure 3**. According to the model, the optimal course of treatment for moderate-to-severe TBI was 12.2 sessions of HBO_2, while the optimal prognosis for moderate and severe TBI was 14 and 21.6 hyperbaric sessions, respectively.

Table 1 | Baseline demographics and injury characteristics for favorable and unfavorable groups

Variables	Total	Outcome		*P* value
		Favorable (*n* = 83)	Unfavorable (*n* = 50)	
Age (yr, median (IQR))	49 (39.5–56.5)	47 (39, 53)	52 (44, 58)	0.034*
Sex				
Male	94 (70.7)	62 (74.7)	32 (64.0)	0.264
Female	39 (29.3)	21 (25.3)	18 (36.0)	
Education level				
<9 yr	97 (72.9)	56 (67.5)	41 (82.0)	0.068
≥9 yr	36 (27.1)	27 (32.5)	9 (18.0)	
Employment status				
Employed	127 (95.5)	80 (96.4)	47 (94.0)	0.833
Unemployed	6 (4.5)	3 (3.6)	3 (6.0)	
Drinking history				
≥10 yr	19 (14.3)	12 (14.5)	7 (14.0)	
Seldom	25 (18.8)	16 (19.3)	9 (18.0)	0.977
Never	89 (66.9)	55 (66.3)	34 (68.0)	
Injury cause				
Traffic accidents	71 (53.4)	47 (56.6)	24 (48.0)	
Falls	53 (39.8)	33 (39.8)	20 (40.0)	0.166
Other	9 (6.8)	3 (3.6)	6 (12.0)	
GCS score (mean±SD)				
Total	7.18±2.16	7.56±2.07	6.54±2.17	0.0083*
Moderate (9–12)	10.0±1.07	10.10±1.14	9.80±0.92	0.447
Severe (3–8)	6.32±1.60	6.71±1.54	5.73±1.52	0.002*
Interventions				
Tracheotomy				0.053
Yes	40 (30.1)	20 (24.1)	20 (40.0)	
No	93 (69.9)	63 (75.9)	30 (60.0)	
Neurosurgical interventions				0.66
Yes	83 (62.4)	53 (63.9)	30 (60)	
No	50 (37.6)	30 (36.1)	20 (40)	
Length of ICU stay [median (IQR)]	6.0 (3, 6)	6 (4, 9.75)	11 (6, 16.75)	< 0.05*
HBO_2 interventions (mean±SD)				
HBO_2 sessions	25.7±19.7	21.5±14.8	32.5±24.5	0.002*
HBO_2 initiation time	27.9±15.8	25.6±15.9	31.7±14.9	0.030*

Favorable outcomes indicating DRS scores 0–3; Unfavorable outcomes indicating DRS scores 4–30. Except for annotations, all other data are presented in the form of number (percentage). Outcomes group differences were determined by chi-squared test or Fisher exact test. Statistical significance was determined as *$P < 0.05$. GCS: Glasgow Coma Scale; HBO_2: hyperbaric oxygen; ICU: intensive care unit; IQR: interquartile range.

Table 2 | The severity of TBI and the outcomes by the Glasgow Outcome Scale Score and Disability Rating Scale

Injury severity	STBI (*n* = 102)	MTBI (*n* = 31)	Total (*n* = 133)
Disability Rating Scale			
Dead (30)	8 (7.8)	1 (3.2)	9 (6.8)
Extreme vegetative state/vegetative state (22–29)	2 (2.0)	0	2 (1.5)
Extremely severe/severe (12–21)	5 (4.9)	0	5 (3.7)
Moderately severe/moderate (4–11)	25 (24.5)	9 (29.0)	34 (25.6)
Partial/mild (1–3)	36 (35.3)	6 (19.4)	42 (31.6)
None (0)	26 (25.5)	15 (48.4)	41 (30.8)
Glasgow Outcome Scale			
Dead (1)	8 (7.8)	1 (3.2)	9 (6.8)
Vegetative (2)	1 (1.0)	0	1 (0.7)
Severe disability (3)	12 (11.8)	1 (3.2)	13 (9.8)
Moderate disability (4)	26 (25.5)	11 (35.5)	37 (27.8)
Good recovery (5)	55 (53.9)	18 (58.1)	73 (54.9)

Data are presented as number (percentage). MTBI: Moderate traumatic brain injury; STBI: severe traumatic brain injury; TBI: traumatic brain injury.

Table 3 | Logistic regression analysis of the probability of a favorable over 5-year prognosis with each potential risk factor

			Univariable analysis		Multivariable analysis	
Variables	Unfavorable group	Favorable group	Odds ratio (95% confidence interval)	*P* value	Odds ratio (95% confidence interval)	*P* value
Age (yr)	49.2±10.8	45.0±11.1	0.96 (0.93–1.00)	0.037	0.96 (0.92–0.99)	0.031
GCS score	6.5±2.2	7.6±2.1	1.26 (1.07–1.52)	0.009	1.19 (0.98–1.46)	0.081
Length of ICU stay (d)	10.5±8.8	5.8±5.7	0.91 (0.86–0.96)	0.001	0.94 (0.88–0.99)	0.034
HBO_2 sessions	32.5±24.5	21.5±14.8	0.97 (0.95–0.99)	0.004	0.97 (0.95–0.99)	0.005
HBO_2 initiation timing (d)	31.7±14.9	25.6±15.9	0.98 (0.95–1.00)	0.035	0.99 (0.96–1.02)	0.518

Data are presented as mean ± SD. GCS: Glasgow Coma Scale; HBO_2: hyperbaric oxygen; ICU: intensive care unit.

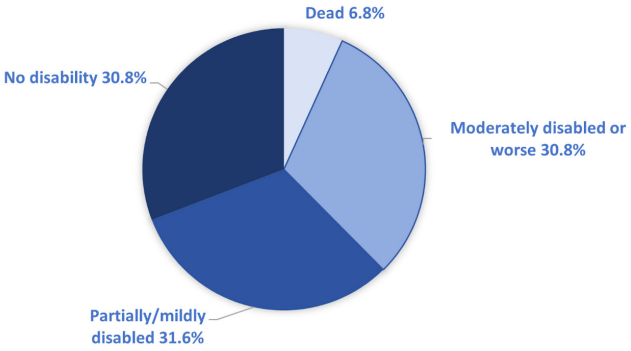

Figure 1 | Long-term prognosis for patients with moderate-to-severe traumatic brain injury.

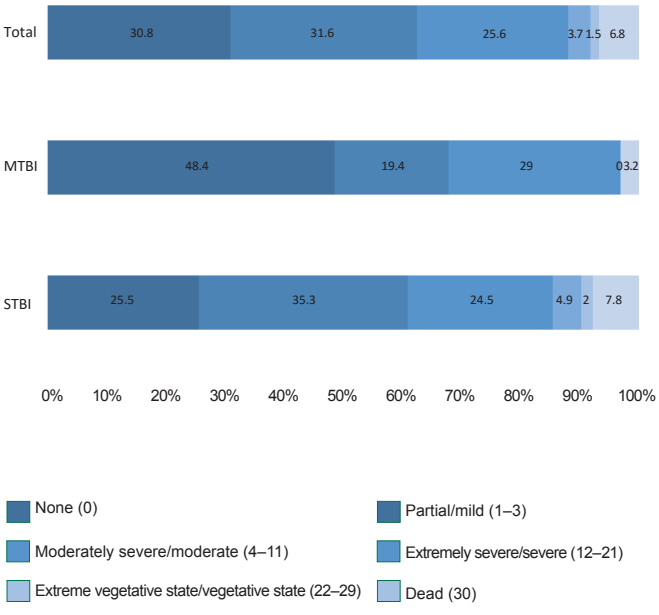

Figure 2 | Distribution of total scores on the disability rating scale for patients with moderate-to-severe traumatic brain injury.
MTBI: Moderate traumatic brain injury; STBI: severe traumatic brain injury.

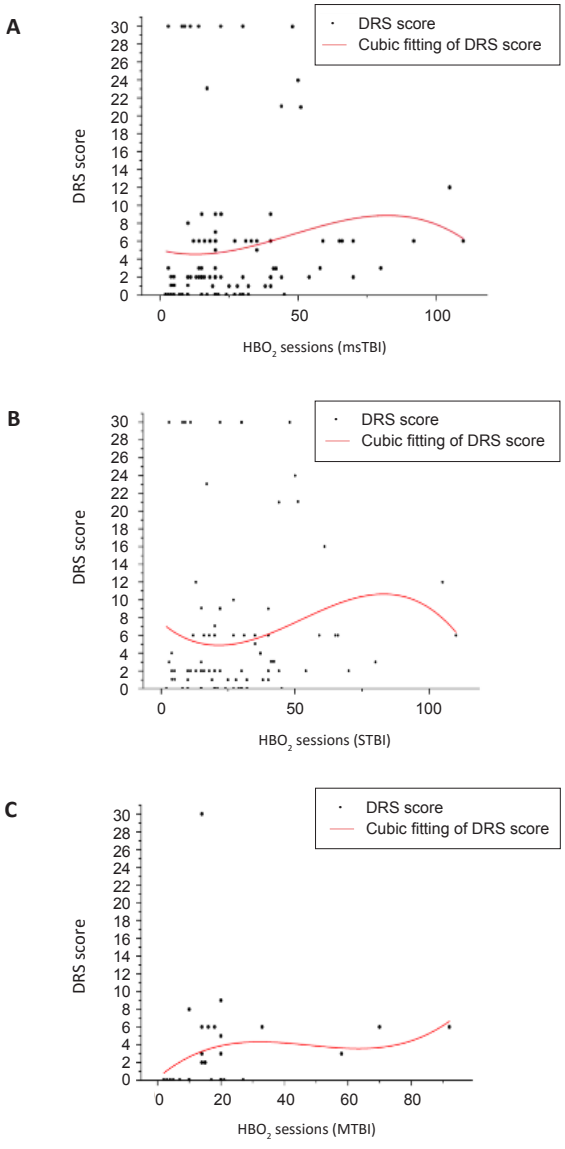

Figure 3 | Relationship between the number of HBO_2 sessions and long-term prognosis (DRS score) in msTBI.
(A) The relationship between the number of HBO_2 sessions and DRS scores in all msTBI patients. (B) The relationship between DRS scores and the number of HBO_2 sessions in STBI patients. (C) The relationship between DRS scores and the number of HBO_2 sessions in MTBI patients. DRS: Disability Rating Scale; HBO_2: hyperbaric oxygen; MTBI: moderate traumatic brain injury; msTBI: moderate-to-severe traumatic brain injury; STBI: severe traumatic brain injury.

Discussion

Comparing the percentage of survivors with moderately disabled or worse 5 years post-TBI (without HBO_2) reported by Whitnall et al.[9] and Corrigan et al.[8] at 53% and 57%, respectively, and the mortality rate at 24% and 20.6%, respectively, the proportion of those with moderately disabled or worse (DRS scores 4–29) and the mortality rate in the present study were significantly lower, at 33.1% (41/124) and 6.8%, respectively. This result differed considerably from the concerns and suspicions that HBO_2 would reduce TBI-related mortality while increasing survivors of severely disabled and vegetative individuals.[27] Therefore, we hypothesized that HBO_2 may assist reduce the public health burden for moderate-to-severe TBI survivors by lowering death and disability levels following injury and increasing the proportion of those with mild disability or full recovery. Nevertheless, it is indisputable that variations in methodological and demographic aspects of injuries amongst studies could account for the disparity in results. While this follow-up study found that many patients (82.7%) treated with HBO_2 were able to achieve living independence (Glasgow Outcome Scale ≥ 4) 5–8 years after their injury, it is critical to avoid having an optimistic outlook on the prognosis for moderate-to-severe TBI, as one-third of survivors still had moderate disability or worse.

Comparing the outcomes of moderate TBI, the inferior long-term prognosis of severe TBI was assessed in the current study as more death (7.8% *vs*. 3.2%), more survivors with moderate disability or worse (31.4% *vs*. 29%), and a lower percentage of favorable prognosis (60.8% *vs*. 67.8%). It was heartening to note that our follow-up study observed that among 102 patients with severe TBI (GCS scores of 3–8), 26 individuals (25.5%) achieved long-term favorable recovery, being able to reintegrate into society without employment limitations or residual disabilities. Compared with the unfavorable group, the favorable group has a 26% greater likelihood of having a higher GCS score than the unfavorable group. This result was consistent with the findings of numerous studies.[1-3,5,15] However, compared with the unfavorable group, the favorable group has a 19% greater likelihood of having a higher GCS score than the unfavorable group, with accompanying variables adjusted per the multivariable analysis. Prior studies have shown that long-term TBI-related outcomes were found to be significantly correlated with factors such as aggressive treatment, sustained functional rehabilitation, and psychological therapies, rather than the severity of the initial injury, which appeared to be less significant.[7-9] Our findings were consistent with the conclusions of these studies, so we hypothesized that a comprehensive therapeutic strategy of aggressive treatment and ongoing rehabilitation may be able to substantially mitigate the negative functional impact of severe TBI on patients and eventually improve their long-term functional prognosis.

Logistic analysis revealed that age and length of intensive care unit stay were independent indicators in the long-term prognosis of moderate-to-severe TBI. In the current study, up to 43.9% of patients aged 51–60 years had approximately twice the mortality (9% *vs*. 5%) and disability rate (DRS scores 4–29 [40% *vs*. 24%]) as those aged 18–50 years. These findings were consistent with a number of previous research that found aging to be harmful to functional recovery in TBI patients.[1,3,5-7] The vast majority of patients in this study (81.2%) had been admitted to the intensive care unit. Based on clinical experience and study findings, we hypothesized that more severe intracranial and/or extracranial injuries, as well as a variety of complex complications occurring during this period, would result in longer intensive care unit stays[36]; consequently, prolonged hospitalization in the intensive care unit was associated with a poor long-term prognosis for patients.

Multiple HBO_2 treatments, rather than a single therapy, appear to reduce cerebral edema, decrease neuroinflammation and neuronal apoptosis, and enhance neural regeneration in the field of TBI.[15] However, HBO_2 treatment protocols for TBI patients have varied substantially in previous clinical studies,[15-18,21,23,26,29,30,37] and the specific HBO_2 regimens from which TBI patients are most likely to benefit remain to be further elucidated. Our data indicated that the number of hyperbaric sessions was an independent risk factor for moderate-to-severe TBI over the long term, with the optimal number of sessions (2.0 atmosphere absolute) for moderate and severe TBI being 14 and 21.6 treatments, respectively, and the risk of an unfavorable outcome increasing by 3% for each additional session beyond the optimal number. A case-control study yielded similar conclusions, finding that 20 consecutive HBO_2 (2.0 atmosphere absolute) were more beneficial than 10 sessions in alleviating cognitive deficits in individuals with moderate-to-severe TBI.[16] One of the vital adverse effects of HBO_2 is cerebral oxygen toxicity, which is especially prevalent in patients with fragility, concurrent comorbidities, and moderate-to-severe TBI.[25,26] We postulated that a certain dose threshold of HBO_2 exposure might not interfere with the body's natural oxidative and antioxidant homeostasis; however, excessive HBO_2 exposure may cause a dysregulation of antioxidant homeostasis and a continued accumulation of cerebral oxygen toxicity, potentially exacerbating primary brain damage. This finding suggested that HBO_2, similar to many drugs, is beneficial to TBI patients at appropriate exposure doses, while overdose may cause additional damage or even aggravate pre-existing injury, implying that clinicians, particularly those involved in HBO_2, should carefully consider the potential adverse effects of HBO_2 overexposure when providing HBO_2 professional counseling to patients or their families with moderate-to-severe TBI.

Our findings shed new light on the relationship between hyperbaric sessions and long-term outcomes in moderate-to-severe TBI and highlighted the importance of administering individualized hyperbaric protocols for moderate-to-severe TBI. Treatment regimens that desperately increase the number of hyperbaric sessions in pursuit of favorable outcomes should be avoided and did not appear to be recommended. Given the heterogeneity in premorbid health status, co-morbidities, and severity of TBI, future study is essential to discover the precise HBO_2 exposure pressures and hyperbaric sessions that might benefit those particular survivors.

Previous studies have suggested that initiating HBO_2 in the early stages of TBI reduced neuronal apoptosis and attenuated

secondary brain injury, whereas delayed intervention tended to be less effective.[11-14,19] However, delays in hyperbaric treatments following moderate-to-severe TBI in our study, would have no long-term influence on global outcomes. Baratz-Goldstein et al.[38] reported similar findings in mice with immediate and delayed HBO_2 treatment for TBI. Numerous clinical trials have demonstrated the beneficial benefits of HBO_2 on brain recovery, whether the time period is 27 years after injury (sequelae phase) or 11 hours after TBI (hyper-acute phase).[16,18,37,39]

Several limitations should be acknowledged and considered when interpreting the results of the present study. To begin with, because we did not track community-home rehabilitation following discharge, which could affect prognosis in the long run, it is plausible that the results were influenced by a sequence of successive restorations. Second, due to the small sample size in this study, there will definitely be follow-up losses. The loss-to-follow-up rate was 8.3%, which was lower than in previous research.[2,7,9] Therefore, the findings should be interpreted with caution due to the insufficient data and the risk of selection bias. Third, this was a retrospective study that could not provide a definitive assessment of causality, thus the findings should be viewed with caution. Lastly, a greater percentage of TBI survivors reported extended functional fluctuations following their injury[7-9,40,41]; however, the results of our investigation did not identify functional fluctuations that would have affected the scale assessment.

The outcomes of this observational study revealed that HBO_2 adjunctive therapy could improve the prognosis of moderate-to-severe TBI by lowering mortality and disability levels, increasing the population with partial/mild disability or no disability. Delays in hyperbaric intervention following moderate-to-severe TBI would have no long-term influence on outcomes. In patients with moderate-to-severe TBI, older age at the time of injury, longer intensive care unit stays, and overexposure to HBO_2 may lead to a poor long-term prognosis. Patients with moderate-to-severe TBI should be given a tailored HBO_2 treatment to reduce the potentially harmful effects associated with excessive HBO_2 exposure.

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Additional files:

Additional Table 1: *Co-morbidities and concomitant injuries for favorable and unfavorable groups.*

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Additional Table 1: Co-morbidities and concomitant injuries for favorable and unfavorable groups

Variables	Total	Outcome		*P*-value
		Favorable (*n*=83)	Unfavorable (*n*=50)	
Co-morbidities				
Hypertension				0.2255
Yes	11 (8.3)	5 (6.0)	6 (12.0)	
No	122 (91.7)	78 (94.0)	44 (88.0)	
Diabetes	5	0	5	NA
Preexcitation syndrome	2	0	2	NA
Atrial fibrillation	2	0	2	NA
Coronary atherosclerotic heart disease	1	0	1	NA
Concomitant injuries				
Thoracic injury				0.2435
Yes	45 (33.8)	25 (30.1)	20 (40.0)	
No	88 (66.2)	58 (69.9)	30 (60.0)	
Limbs injury				0.05272
Yes	40 (30.1)	20 (24.1)	20 (40.0)	
No	93 (69.9)	63 (75.9)	30 (60.0)	
Spinal injury				0.6491
Yes	24 (18.0)	14 (16.9)	10 (20.0)	
No	109 (82.0)	69 (83.1)	40 (80.0)	
Pelvic injury				0.1104
Yes	14 (10.5)	6 (7.2)	8 (50.0)	
No	119 (89.5)	77 (92.8)	42 (50.0)	

Favorable outcomes indicating DRS scores 0–3; unfavorable outcomes indicating DRS scores 4–30. Data are presented in the form of number (percentage). Outcomes group differences were determined by chi-squared test or Fisher exact test. DRS: Disability Rating Scale; NA: not applicable.