Am J Transl Res 2026;18(5):4326-4345
www.ajtr.org /ISSN:1943-8141/AJTR0172592

Original Article

Impact of hyperbaric oxygen therapy on serum lipid profiles and cognitive recovery in patients with post-stroke cognitive impairment: a retrospective cohort study

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Received March 12, 2026; Accepted April 27, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: Background: Post-stroke cognitive impairment (PSCI) affects patients' quality of life, with hyperlipidemia being a key modifiable risk factor. Hyperbaric oxygen therapy (HBOT) may confer neuroprotection, but its effects on lipid metabolism and cognitive recovery in PSCI remain unclear. Objective: To evaluate the effects of HBOT combined with conventional therapy on lipid profiles and cognitive function in PSCI patients. Methods: This retrospective cohort study included 115 PSCI patients divided into control (conventional treatment, n = 58) and HBOT (additional HBOT, n = 57) groups. Propensity score matching (PSM) balances baseline confounders were assessed. Outcomes included lipid parameters, cognitive scores [Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE)], and inflammatory markers. Results: The HBOT group showed significantly greater improvement in MoCA scores (4.00 ± 1.86 vs. 1.63 ± 1.79 points; mean difference 2.37, 95% CI 1.61-3.13, $P < 0.001$) and greater LDL-C reduction (-0.92 ± 0.54 vs. -0.35 ± 0.47 mmol/L; mean difference -0.57, 95% CI -0.78 to -0.36, $P < 0.001$). HBOT was independently associated with cognitive improvement (OR = 3.45, 95% CI 1.49-8.02), with LDL-C reduction mediating 21.07% of the cognitive benefit. Conclusion: HBOT combined with conventional rehabilitation significantly improves lipid metabolism and cognitive recovery in PSCI patients, potentially through lipid regulation and neurovascular protection.

Keywords: Hyperbaric oxygen therapy, post-stroke cognitive impairment, lipid, cognitive function, propensity score matching, retrospective cohort study

Introduction

Post-Stroke Cognitive Impairment (PSCI) is one of the most common complications following a cerebrovascular event, and its incidence has been increasing annually as the survival period of stroke patients has been prolonged [1, 2]. Epidemiological data show that approximately one-third of stroke survivors will exhibit varying degrees of cognitive decline within a few months after the onset of the disease, and this proportion is even higher in patients with recurrent and insidious strokes [3, 4]. PSCI not only severely affects the daily living abilities and social participation of patients but it also imposes a heavy burden on families and the medical care system [5]. What's more, the decline in cognitive function has a complex bidirectional relationship with the risk of stroke recurrence, leading patients into a vicious cycle of difficulties [6, 7]. Therefore, exploring intervention strategies to effectively delay or even reverse the progression of PSCI has become a key issue that urgently needs to be addressed in neurorehabilitation [8, 9].

https://doi.org/10.62347/ML0M4923

Among the numerous risk factors for PSCI, lipid metabolic disorders are considered one of the core controllable factors [10, 11]. Hyperlipidemia directly or indirectly affects neuronal survival and synaptic plasticity by promoting atherosclerosis, impairing cerebral blood flow, and triggering neuroinflammatory responses [12, 13]. Clinical observations have revealed that patients with PSCI accompanied by hypercholesterolemia often exhibit more prominent impairments in memory and executive functions. Although the drugs can exert cardiovascular protection by reducing low-density lipoprotein cholesterol (LDL-C), their effects on already-formed cognitive impairment are often limited and delayed [14, 15]. This suggests that, given lipid-lowering treatment, additional methods with greater neuro-repair potential may be needed to break the deadlock of the continuous decline in cognitive function.

Hyperbaric Oxygen Therapy (HBOT), a treatment that improves ischemic and hypoxic conditions by increasing the partial pressure of oxygen in tissues, has gradually gained attention in the field of neurological diseases in recent years [16, 17]. Its basic principle lies in inhaling pure oxygen in an environment with a pressure higher than the absolute atmospheric pressure, which can significantly increase the physical dissolved oxygen content in the plasma, bypassing the oxygen-carrying capacity of damaged red blood cells, and directly supplying oxygen to the hypoxic brain tissues [18, 19]. This mechanism is particularly important for neurons in the “ischemic penumbra” after stroke and may reshape neural function by improving energy metabolism, inhibiting apoptosis, and promoting neural stem cell proliferation [20, 21]. In clinical practice, we have observed that some stroke patients who received HBOT not only recovered their motor limb function but also experienced unexpected improvements in memory, attention, and executive function. At the same time, the lipid profile test results of these patients often show a more favorable trend, prompting us to consider the quesion: Does HBOT, by regulating the lipid metabolic pathway, indirectly or directly promote the recovery of cognitive function?

At present, there is insufficient research on the impact of HBOT combined with conventional rehabilitation on the lipid profile and cognitive function of patients with PSCI. On the one hand, previous studies have mostly focused on assessing a single outcome indicator, lacking an integrated analysis of the multi-dimensional indicators of lipids and changes in cognitive dimensions [22, 23]. On the other hand, due to the long duration of HBOT treatment and the significant heterogeneity in patients’ baselines, controlling confounding factors and clarifying causal relationships have always been challenges in clinical research design [24, 25]. This study was initiated in response to the aforementioned clinical background and research gaps. Our aim was to conduct a retrospective cohort study, using propensity score matching (PSM) to balance confounding factors between groups, combined with generalized estimating equations (GEE) to handle longitudinal data, and introduce a mediation effect analysis model, to deeply explore the impact of HBOT on the serum lipid profile and cognitive function of patients with PSCI, as well as the underlying mechanisms. The innovation points of this study mainly lie in three aspects: First, at the effect verification level, we for the first time combined the detailed classification of lipid profiles [including apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), etc.] with multi-dimensional cognitive assessment, attempting to depict the comprehensive profile of HBOT’s effect; Second, at the analysis method level, we comprehensively utilized multivariate regression, sensitivity analysis, and GEE, forming a multi-level statistical evidence chain from baseline matching to longitudinal tracking, from association verification to causal inference, to enhance the robustness of the conclusion; Third, at the mechanism exploration level, by constructing a mediation effect model, we attempted to quantify the contribution of lipid improvement in cognitive benefits, providing clinical clues for subsequent mechanism research. We hope that through this study, we can provide a new evidence-based basis for the comprehensive clinical management of PSCI and promote the individualized application of HBOT in neurorehabilitation.

Research subjects and research methods

Research subjects

This was a single-center retrospective cohort study that continuously enrolled patients with

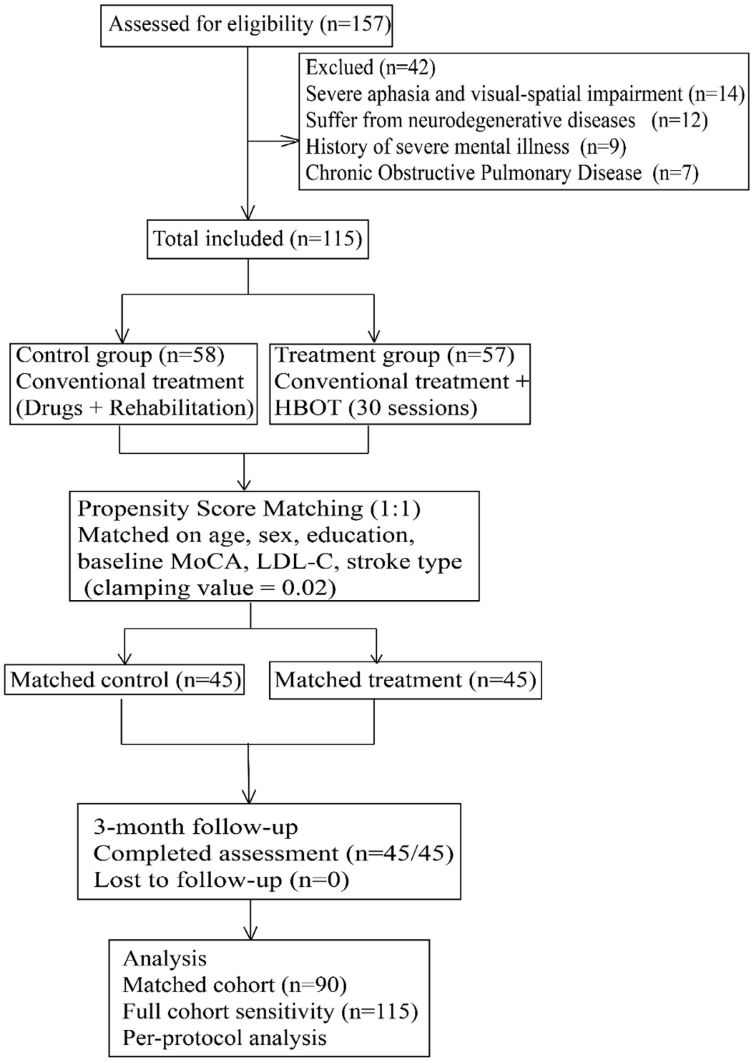

Figure 1. Flowchart HBOT is Hyperbaric oxygen therapy. LDL-C is low-density lipoprotein cholesterol.

PSCI who visited the Neurology and Rehabilitation Departments of Pudong New Area People's Hospital in Shanghai from January 2024 to June 2025. The study subjects were adult patients with a confirmed history of stroke, as determined by head computed tomography or magnetic resonance imaging, who met the PSCI diagnostic criteria in the "Expert Consensus on Management of PSCI 2021". A total of 157 cases were screened, and finally, 115 patients who met the study requirements were included. They were divided into the treatment group (57 cases) and the control group (58 cases) based on whether they received HBOT. To ensure the comparability of the two groups at the baseline, all included subjects needed to be aged between 45 and 80 years, have a stroke duration of 3 months to 2 years, and have a Montreal Cognitive Assessment Scale (MoCA) score between 18 and 25, indicating mild to moderate cognitive impairment [26], as shown in **Figure 1**.

Exclusion and inclusion criteria

Inclusion Criteria [27, 28]: (1) Age 45-80 years old; (2) First-onset ischemic or hemorrhagic stroke, with a disease duration of 3 months to 2 years, confirmed by imaging, stable vital signs, clear consciousness, and able to cooperate with assessment and training; (3) Meets the PSCI diagnostic criteria as stipulated in the "Expert Consensus on Management of PSCI 2021", with a MoCA score of 18-25, indicating mild to moderate cognitive impairment; (4) Those who are scheduled to receive HBOT must undergo otolaryngological consultation to rule out eustachian tube dysfunction and ensure tolerance to pressure changes.

Exclusion Criteria [29, 30]: (1) Severe aphasia, visual or auditory impairment, which affects the cognitive assessment; (2) Comorbid with neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease; (3) History of severe mental illness or currently taking antipsychotic drugs; (4) Chronic obstructive pulmonary disease, uncontrolled heart failure, malignant arrhythmia or hemodynamic instability; (5) Active malignant tumors or expected survival period < 6 months; (6) Pregnant or lactating; (7) Participated in other clinical trials within the past 3 months; (8) In the combined group, those who interrupted HBOT for a cumulative total of ≥ 5 times or experienced adverse events such as severe decompression sickness or oxygen poisoning were excluded; (9) In

the control group, those who adjusted the routine plan or actively received HBOT were excluded.

Research plan

This study analyzed the clinical data of stroke patients through retrospective medical record review and data extraction. Based on whether they received HBOT, the patients were divided into the control and treatment groups. The medical records of both groups showed that they all received the basic intervention plan of routine secondary prevention and rehabilitation treatment after stroke.

(1) The treatment plan records of the control group indicated that the intervention model was the widely used conventional comprehensive rehabilitation model in clinical practice, which specifically included two major parts: drug treatment and rehabilitation training. In terms of drug treatment, according to the doctor's orders, some patients used the calcium channel blocker nimodipine to regulate cerebral blood flow; at the same time, brain protein hydrolysate and cytidine diphosphate choline were combined to promote nerve repair. Regarding dyslipidemia, the medical records showed that statin lipid-lowering drugs were selected based on the patient's baseline lipid levels and clinical indications [31, 32]. The records for the rehabilitation training component came from the rehabilitation therapists' work logs. The log showed that the training implemented by the professional treatment team covered limb balance, gait correction, language function, and training in daily living activities. The records indicated that the rehabilitation training was conducted 5 times per week, each lasting 60 minutes, and the total intervention duration was 3 months.

(2) The intervention measures recorded for the treatment group show that, in addition to the conventional rehabilitation treatment, patients also received HBOT. The HBOT equipment was recorded as the Shanghai-made SHC2600/8000 type medical air pressurization chamber. The recorded treatment parameters indicated that the treatment pressure was set to 2.0 absolute atmospheres. The recorded treatment process included three stages: pressure increase, stable-pressure oxygen inhalation, and pressure reduction. The pressure increase stage lasted for 20 minutes, using compressed air to increase pressure at a constant rate; the stable pressure stage involved the patient wearing a mask to breathe pure oxygen (with oxygen concentration recorded > 99.9%), and the oxygen inhalation lasted for 60 minutes; the pressure reduction stage also lasted for 20 minutes, reducing pressure at a constant rate to normal pressure. The recorded treatment frequency was once a day from Monday to Friday, with 10 treatments counted as one course; a total of 3 courses (30 treatments) were completed. The entire intervention period was recorded as approximately 3 months [33, 34].

The medical records and nursing notes also show that all hyperbaric oxygen treatments were carried out under the supervision of medical staff. The pre-cabin health education, electrocardiogram monitoring within the cabin, emergency preparedness, and the rest process in the observation area after the treatment are all documented. The medical records of the treatment group also include consultations with the otolaryngology department prior to enrollment to assess their tolerance to pressure changes. Throughout the intervention period, the routine medication and rehabilitation training records of the treatment group patients showed that they all adhered to the plan, and hyperbaric oxygen treatment was used as an additional intervention rather than a substitute. Based on the retrospective data, this stratified intervention design provides a basis for evaluating the incremental value of HBOT and analyzing its synergistic mechanism.

Hyperbaric oxygen therapy is conducted using the SHC2600/8000 medical air pressurization chamber produced in Shanghai. The treatment pressure is set at 2.0 absolute atmospheres (0.2 MPa). The specific operation process is as follows: After the patient enters the chamber, compressed air is used to gradually increase the pressure. The pressure increase process lasts for 20 minutes, during which the first 5 minutes are the pressure adaptation period (no oxygen inhalation), and then the patient wears the mask to start breathing pure oxygen (oxygen concentration > 99.9%) and continues to increase the pressure to the target pressure. After entering the stable pressure stage, the patient continues to inhale oxygen through the mask for 60 minutes without interruption. Then, the decompression stage begins, and the

patient continues to inhale oxygen while gradually reducing the pressure for 20 minutes until the pressure inside the chamber returns to normal pressure and oxygen inhalation stops. The treatment frequency is once a day from Monday to Friday each week, with 10 sessions constituting one treatment course. A total of 3 treatment courses (cumulatively 30 sessions) are completed. The entire treatment process is monitored by dedicated medical staff throughout, and all operations are carried out in accordance with the "Clinical Application Technical Specifications for Hyperbaric Oxygen".

Observation indicators

All indicators were collected at the baseline period (within 24 hours before the start of treatment) and after the intervention (48 hours after the last treatment). This was done to ensure consistency in the assessment time points.

The observed indicators in this study span multiple dimensions, including lipid metabolism, cognitive function, inflammatory response, neurotrophic status, and safety. The aim is to comprehensively evaluate the impact of HBOT on patients with PSCI and its potential mechanism.

(1) Lipid metabolism indicators are the focus of this study, and a total of six detection items were included. Total cholesterol (TC), triglycerides (TG), LDL-C, high-density lipoprotein cholesterol (HDL-C), ApoA1, and ApoB - these six lipid indicators were collected from venous blood in the fasting state in the morning. The lipid profile test was conducted using the Roche Cobas 8000 series fully automatic biochemical analyzer (c702 module), with the corresponding reagent kits being Roche's original reagents (total cholesterol: cholesterol oxidase - peroxidase - 4-aminoantipyrine phenol method, batch number 20231201; TG: glycerol-3-phosphate oxidase-peroxidase-aminoantipyrine phenol method, batch number 20231205; LDL-C: direct method, batch number 20231210; HDL-C: direct method, batch number 20231210; Apo A1 and Apo B: immunoturbidimetry method, batch number 2023-1215). Before the test, Roche's original calibrators were used for two-point calibration, and high- and low-level quality control samples (Roche PreciControl series) were simultaneously measured in each test batch. The intra-batch coefficient of variation was 1.2%-2.5%, and the inter-batch coefficient of variation was 2.1%-3.8%, both of which were in accordance with the reagent kit instructions and clinical laboratory quality control standards. The lipid profile test was conducted by collecting venous blood in the fasting state in the early morning. The test was performed once at the baseline (24 hours before the start of treatment) and once again after the intervention ended (48 hours after the last treatment). All blood samples were collected between 7:00 and 8:00 in the morning. Patients were required to fast for at least 8 hours to ensure the standardization of the testing conditions and the comparability of the results.

(2) The cognitive function assessment was conducted using the internationally recognized MoCA and the Mini-Mental State Examination (MMSE). The MoCA covers various cognitive domains such as attention and concentration, executive function, memory, language, visuospatial skills, abstract thinking, calculation, and orientation, and is particularly sensitive to vascular cognitive impairment, capable of detecting subtle changes in mild cognitive impairment [34, 35]. The MMSE, as a classic cognitive screening tool, is simple to administer and quick to complete, focusing on the assessment of orientation, memory, attention, and language functions, thereby facilitating rapid clinical understanding of the patient's overall cognitive level [36]. The two evaluations were independently conducted by two neuro-psychological assessors who had received unified training at the baseline and after 3 months of treatment. The assessors were unaware of the patient groups. Before the formal assessment, the two assessors conducted a pre-assessment on 20 non-participating patients and calculated the intraclass correlation coefficient (ICC) to assess inter-rater reliability. The results showed that the ICC for the MoCA assessment was 0.94 (95% CI 0.88-0.97), and the ICC for the MMSE assessment was 0.92 (95% CI 0.85-0.96), indicating good consistency among assessors. During the formal assessment, every 10th patient was randomly selected by one assessor for synchronous re-evaluation by another assessor to ensure the continuous stability of assessment quality.

(3) Inflammatory-related indicators include high-sensitivity C-reactive protein (hs-CRP),

homocysteine (Hcy), and interleukin-6 (IL-6). The combined detection of these three indicators helps reveal whether HBOT exerts neuroprotective effects by inhibiting the inflammatory pathway.

(4) The assessment of neurotrophic status selects serum brain-derived neurotrophic factor (BDNF) as the marker.

(5) Safety observation runs through the entire research process, focusing on adverse events related to HBOT and abnormal situations during the routine rehabilitation process. This includes middle ear barotrauma, manifested as ear pain, tympanic membrane congestion or perforation; oxygen toxicity, which can affect the central nervous system and present as facial muscle twitching, visual field reduction, hearing changes or generalized tonic-clonic seizures, or it can affect the lungs as chest pain, cough and breathing difficulties; blood pressure fluctuations, including hypertensive emergencies or orthostatic hypotension; and acute decline in cognitive function, which is dynamically monitored through the MMSE for [37]. All adverse events are recorded in detail, including the time of occurrence, clinical manifestations, treatment measures, and outcomes, to comprehensively evaluate the clinical safety of the treatment plan. During the treatment period, the cabin is equipped with electrocardiogram monitoring equipment and emergency medicines, and is continuously monitored by dedicated medical staff. If the patient experiences severe ear pain, chest tightness, anxiety, or changes in consciousness, the pressurization process will be halted immediately, or an emergency plan will be initiated. If necessary, the treatment will be terminated, and the patient will be urgently evacuated from the cabin. All adverse events are meticulously recorded, including the time of occurrence, clinical manifestations, treatment measures, and outcomes.

Sample size calculation

This study was a retrospective design. The sample size was determined based on the actual cases that met the inclusion and exclusion criteria, collected continuously from January 2024 to June 2025. A total of 115 patients were included, and after PSM, there were 45 cases in each group. Since no prior sample size estimation was conducted, we performed a post hoc power analysis to assess whether the current sample size was sufficient to detect key intergroup differences, focusing on the primary outcome measure (MoCA score change). Based on the minimum clinically important difference (2.5 points) of the MoCA score after treatment in both groups in the pre-analysis and a combined standard deviation (4.2 points), the calculated effect size of Cohen's d was 0.60. Under the two-sided test level $\alpha = 0.05$ and with 45 cases in each group, the statistical power (1-β) of the current sample, calculated using G*Power software, was 0.86, indicating that this study has an 86% confidence level to detect the true differences in cognitive improvement between the two groups. For lipid indicators, taking the change in LDL-C as an example, the confidence level reached 0.82 based on the observed effect size of 0.55. The post hoc power analysis confirmed that, although the sample size was limited by the retrospective study's circumstances, the current sample size still had sufficient power to verify the main research hypothesis, and the conclusion was reliable.

Statistical methods

First, a normality test was conducted for the continuous variables. For normally distributed data, the mean ± standard deviation was used to represent them, and the independent-samples t-test was employed for comparisons between groups; for non-normally distributed data, the median (interquartile range) was used to represent them, and the Mann-Whitney U test was used. For categorical data, frequencies (percentages) were used to summarize them, and the chi-square or Fisher's exact test was used to compare groups. Multivariate Logistic regression was used to adjust for confounding factors and assess the associations between HBOT and lipid levels and cognitive improvement odds ratios (ORs) and 95% CIs. To utilize longitudinal data, GEE was used to evaluate the interaction effect of time and group, with an unstructured matrix set and the connection function selected based on the data type. Sensitivity analysis was conducted by excluding those with poor compliance, changing the PSM matching ratio, and calculating the E-value. The propensity score matching method was used to perform 1:1 matching between the two groups of patients, with a

matching coefficient set at 0.02. The matching variables included age, gender, years of education, stroke type (ischemic/hemorrhagic), disease duration, baseline MoCA score, baseline LDL-C level, history of statin use (yes/no), and baseline hs-CRP level. Among them, the history of statin use was included in the matching as a key confounding factor because it may independently affect lipid levels and cardiovascular prognosis; the baseline hs-CRP was included in the matching as an alternative indicator of the inflammatory state to control the potential influence of the inflammatory background on cognitive outcomes. After matching, the degree of overlap between the two groups' scores was evaluated by drawing a propensity score kernel density plot. After matching, each group obtained 45 valid samples. There were no statistically significant differences in all matching variables between the groups ($P > 0.05$), and the absolute value of SMD was less than 0.1, indicating good balance between the groups after matching. Further, an intermediary effect model was used, with the HBOT group as the independent variable, the change in lipid value as the intermediary variable, and the change in MoCA value as the dependent variable. Bootstrap sampling was conducted 1,000 times to calculate the intermediary effect and 95% CI. If the interval does not include 0, the intermediary effect is considered significant. All analyses were completed using SPSS 26.0 and R 4.1.0, with a two-sided significance level of $\alpha = 0.05$.

Ethical statement

This study strictly adhered to the relevant ethical guidelines of the "Helsinki Declaration". The study protocol was approved by the Ethics Committee of Shanghai Pudong New Area People's Hospital (No. 2023-K32). As this was a retrospective observational study, it collected only data generated during routine clinical diagnosis and treatment, without involving additional interventions or invasive examinations. Therefore, the ethics committee waived the requirement for signing an informed consent form. During the research process, all patients' personal information was anonymized, and unique research numbers were used instead of names and hospital numbers to ensure that the data could not be traced back to specific individuals during analysis and publication, thereby fully protecting patients' privacy rights.

Results

Baseline data

Tables 1 and **2** show that before matching, there were 57 cases in the treatment group and 58 cases in the control group. The absolute value range of SMD was between 0.010 and 0.082, with most values being less than 0.1, suggesting that the balance between the two groups was acceptable before matching, but there were still minor fluctuations. After PSM, 45 cases were included in each group. After matching, the differences in all indicators between the two groups (such as age (63.87 ± 7.62 vs. 64.02 ± 7.91, t = 0.09, $P = 0.93$), baseline MoCA (21.38 ± 2.41 vs. 21.33 ± 2.45, t = 0.10, $P = 0.92$), LDL-C (3.45 ± 0.86 vs. 3.43 ± 0.91, t = 0.11, $P = 0.91$)) were further reduced. The *P*-values all approached 1.00, and the absolute values of SMD dropped below 0.053, indicating that the balance between the two groups reached an ideal state after matching, and the comparability was significantly improved.

Before matching, the mean propensity scores of the treatment group and the control group were 0.48 ± 0.12 and 0.52 ± 0.14 respectively, with a standardized mean difference (SMD) of 0.30. After matching, the mean scores of the two groups were 0.49 ± 0.09 and 0.50 ± 0.09 respectively, with the SMD dropping to 0.11. This indicates that matching significantly improved the balance of propensity scores between the groups. There was significant overlap in the score distribution ranges between the two groups (treatment group: 0.31-0.67; control group: 0.33-0.68), and there were no extreme outliers, satisfying the overlap assumption. To further assess potential selection bias, we compared baseline characteristics between successfully matched (n = 90) and unmatched (n = 25) patients, as shown in Table S1. Unmatched patients were significantly older and had significantly higher baseline LDL-C levels, suggesting that the generalizability of our findings to older adults or those with severe hyperlipidemia is limited. Introduce the analysis of unmatched patients and cite Table S1.

Adverse events

During the treatment period (**Table 3**), 9 adverse events occurred in the treatment group (20.0%), compared with 3 in the control group

Table 1. Comparison of baseline data of the first two groups of patients

Indicators	Treatment group (n = 57)	Control group (n = 58)	Mean difference/ratio difference (95% CI)	t/χ^2	*p*	SMD
Age (years)	63.52±7.84	64.17±8.03	-0.65 (-3.55-2.25)	0.44	0.66	-0.082
Male [n (%)]	32 (56.14)	34 (58.62)	-0.02 (-0.21-0.16)	0.07	0.79	-0.050
Years of education (years)	9.47±3.21	9.28±3.45	0.19 (-1.03-1.41)	0.31	0.76	0.057
Ischemic stroke [n (%)]	43 (75.44)	44 (75.86)	-0.00 (-0.16-0.15)	0.00	0.96	-0.010
Course of the disease (months)	8.94±4.37	9.21±4.52	-0.27 (-1.90-1.36)	0.32	0.75	-0.061
Baseline MoCA (Score)	21.46±2.38	21.29±2.51	0.17 (-0.72-1.06)	0.37	0.71	0.069
Baseline MMSE (points)	23.81±2.14	23.67±2.26	0.14 (-0.66-0.94)	0.34	0.73	0.064
TC (mmol/L)	5.43±1.12	5.38±1.18	0.05 (-0.37-0.47)	0.23	0.82	0.043
TG (mmol/L)	2.18±0.76	2.14±0.81	0.04 (-0.25-0.33)	0.27	0.79	0.051
LDL-C (mmol/L)	3.47±0.89	3.42±0.93	0.05 (-0.28-0.38)	0.29	0.77	0.055
HDL-C (mmol/L)	1.08±0.31	1.10±0.33	-0.02 (-0.14-0.10)	0.33	0.74	-0.063
ApoA1 (g/L)	1.16±0.24	1.18±0.26	-0.02 (-0.11-0.07)	0.43	0.67	-0.080
Apo B (g/L)	1.09±0.28	1.07±0.30	0.02 (-0.09-0.13)	0.37	0.71	0.069
Hs-CRP (mg/L)	4.83±1.64	4.71±1.72	0.12 (-0.49-0.73)	0.38	0.70	0.071
Hcy (μmol/)	15.67±4.23	15.38±4.41	0.29 (-1.29-1.87)	0.36	0.72	0.067
IL-6 (pg/mL)	7.84±2.56	7.69±2.63	0.15 (-0.80-1.10)	0.31	0.76	0.058
BDNF (ng/mL)	18.63±4.72	18.91±4.85	-0.28 (-2.03-1.47)	0.31	0.76	-0.059

Note: The measurement data are presented as mean ± standard deviation; MoCA is the Montreal Cognitive Assessment Scale, MMSE is the Mini-Mental State Examination, LDL-C is low-density lipoprotein cholesterol, TC is total cholesterol, TG is Triglyceride, HDL-C is high-density lipoprotein cholesterol, ApoA1 is Apolipoprotein A1, ApoB is Apolipoprotein B, hs-CRP is high-sensitivity C-reactive protein, Hcy is homocysteine, IL-6 is interleukin-6, BDNF is brain-derived neurotrophic factor; SMD is the standardized mean difference, and an absolute value less than 0.1 indicates good inter-group balance.

Table 2. Comparison of baseline data of the two groups of patients after matching

Indicators	Treatment group (n = 45)	Control group (n = 45)	Mean difference/ratio difference (95% CI)	t/χ^2	*p*	SMD
Age (years)	63.87±7.62	64.02±7.91	-0.15 (-3.36-3.06)	0.09	0.93	-0.019
Male [n (%)]	25 (55.56)	26 (57.78)	-0.02 (-0.23-0.18)	0.05	0.83	-0.045
Years of education (years)	9.38±3.14	9.41±3.28	-0.03 (-1.36-1.30)	0.04	0.97	-0.009
Ischemic stroke [n (%)]	34 (75.56)	35 (77.78)	-0.02 (-0.20-0.15)	0.06	0.80	-0.053
Course of the disease (months)	9.05±4.28	9.12±4.41	-0.07 (-1.87-1.73)	0.08	0.94	-0.016
Baseline MoCA (Score)	21.38±2.41	21.33±2.45	0.05 (-0.95-1.05)	0.10	0.92	0.021
Baseline MMSE (points)	23.76±2.18	23.71±2.22	0.05 (-0.86-0.96)	0.11	0.91	0.023
TC (mmol/L)	5.41±1.09	5.39±1.14	0.02 (-0.44-0.48)	0.09	0.93	0.018
TG (mmol/L)	2.16±0.74	2.15±0.79	0.01 (-0.31-0.33)	0.06	0.95	0.013
LDL-C (mmol/L)	3.45±0.86	3.43±0.91	0.02 (-0.35-0.39)	0.11	0.91	0.023
HDL-C (mmol/L)	1.09±0.30	1.10±0.32	-0.01 (-0.14-0.12)	0.15	0.88	-0.032
ApoA1 (g/L)	1.17±0.23	1.18±0.25	-0.01 (-0.11-0.09)	0.20	0.84	-0.042
ApoB (g/L)	1.08±0.27	1.08±0.29	0.00 (-0.12-0.12)	0.00	1.00	0.000
hs-CRP (mg/L)	4.79±1.58	4.75±1.66	0.04 (-0.63-0.71)	0.12	0.91	0.025
Hcy (μmol/L)	15.52±4.18	15.44±4.29	0.08 (-1.67-1.83)	0.09	0.93	0.019
IL-6 (pg/mL)	7.78±2.49	7.73±2.58	0.05 (-1.00-1.10)	0.09	0.93	0.020
BDNF (ng/mL)	18.74±4.68	18.82±4.73	-0.08 (-2.02-1.86)	0.08	0.94	-0.017

Note: MoCA is the Montreal Cognitive Assessment Scale, MMSE is the Mini-Mental State Examination, LDL-C is low-density lipoprotein cholesterol, TC is total cholesterol, TG is Triglyceride, HDL-C is high-density lipoprotein cholesterol, ApoA1 is Apolipoprotein A1, ApoB is Apolipoprotein B. The measurement data are presented as mean ± standard deviation; SMD is the standardized mean difference. After matching, the absolute values of all indicators' SMD were less than 0.1, indicating good inter-group balance.

Table 3. Comparison of adverse event occurrence between the two groups of patients

Type of adverse event	Treatment group (n = 45)	Control group (n = 45)	χ^2	*p*
Middle ear barotrauma	5 (11.1%)	0 (0.0%)	5.29	0.021
Blood pressure fluctuations	3 (6.7%)	2 (4.4%)	0.21	0.645
Mild anxiety	1 (2.2%)	0 (0.0%)	1.01	0.315
Headache	0 (0.0%)	1 (2.2%)	1.01	0.315
Any adverse event	9 (20.0%)	3 (6.7%)	3.53	0.060

Note: The data are presented as the number of cases (percentage); the comparison between groups is conducted using the chi-square test.

Table 4. Comparison of lipid metabolism indicators between the two groups of patients after treatment

Indicators	Treatment group (n = 45)	Control group (n = 45)	Mean difference (95% Confidence Interval)	t	*p*
TC (mmol/L)	4.28±0.87	4.92±0.94	-0.64 (-1.02–0.26)	3.38	0.001
TG (mmol/L)	1.62±0.58	1.98±0.67	-0.36 (-0.62–0.10)	2.74	0.007
LDL-C (mmol/L)	2.53±0.71	3.08±0.82	-0.55 (-0.87–0.23)	3.42	0.001
HDL-C (mmol/L)	1.34±0.28	1.18±0.26	0.16 (0.05-0.27)	2.82	0.006
Apo A1 (g/L)	1.42±0.21	1.26±0.23	0.16 (0.07-0.25)	3.46	0.001
ApoB (g/L)	0.86±0.23	1.02±0.26	-0.16 (-0.26–0.06)	3.12	0.002

Note: MoCA is the Montreal Cognitive Assessment Scale, MMSE is the Mini-Mental State Examination, LDL-C is low-density lipoprotein cholesterol, TC is total cholesterol, TG is Triglyceride, HDL-C is high-density lipoprotein cholesterol, ApoA1 is Apolipoprotein A1, ApoB is Apolipoprotein B.

(6.7%). There was no statistically significant difference in the incidence of any adverse events between the two groups (χ^2 = 3.53, *P* = 0.060). The most common adverse event in the treatment group was middle ear barotrauma, with 5 cases (11.1%) presenting as mild ear pain or tympanic membrane congestion. These symptoms were relieved after training with the eustachian tube pressure regulation. No tympanic membrane perforation or discontinuation of treatment occurred. In the control group, no middle ear barotrauma occurred. There was a statistically significant difference between the two groups (χ^2 = 5.29, *P* = 0.021). Regarding blood pressure fluctuations, 3 cases (6.7%) in the treatment group and 2 cases (4.4%) in the control group were observed after adjusting antihypertensive drugs. Both were stable, and there was no statistically significant difference between the groups (*P* = 0.645). Mild anxiety occurred in only 1 case (2.2%) in the treatment group, and it was relieved after reassurance, allowing the patient to continue the treatment. One case of headache (2.2%) occurred in the control group and was considered related to routine medication. No serious adverse events such as oxygen toxicity, decompression sickness, or acute decline in cognitive function were observed in this study. All adverse events were mild and resolved spontaneously or with simple treatment. No patient terminated the treatment due to adverse events. The above results indicate that the HBOT protocol (2.0 ATA, cumulative 30 sessions) used in this study is well tolerated and safe in patients with mild to moderate PSCI, see **Table 3**.

Lipid metabolism

The lipid profile of the treatment group improved significantly more than that of the control group after treatment (**Table 4**). The TC level of the treatment group (4.28 ± 0.87 mmol/L) was lower than that of the control group (4.92 ± 0.94 mmol/L), with a mean difference of -0.64 (95% CI -1.02 to -0.26), t = 3.38, *P* = 0.001; LDL-C level of the treatment group (2.53 ± 0.71 mmol/L) was lower than that of the control group (3.08 ± 0.82 mmol/L), with a mean difference of -0.55 (95% CI -0.87 to -0.23), t = 3.42, *P* = 0.001; HDL-C level of the treatment group (1.34 ± 0.28 mmol/L) was higher than that of the control group (1.18 ± 0.26 mmol/L), with a mean difference of 0.16 (95% CI 0.05 to 0.27), t = 2.82, *P* = 0.006. The changes in ApoA1 and B were consistent with this.

Table 5. Comparison of cognitive function scores between the two groups of patients after treatment

Indicators	Treatment group (n = 45)	Control group (n = 45)	Mean difference (95% confidence interval)	t	*p*
MoCA (Score)	25.38±2.14	22.96±2.31	2.42 (1.49-3.35)	5.16	< 0.001
MMSE (Score)	27.14±1.86	25.08±2.03	2.06 (1.25-2.87)	5.03	< 0.001

Note: MoCA is the Montreal Cognitive Assessment Scale, MMSE is the Mini-Mental State Examination. After the treatment, the cognitive scores of both groups in the treatment group were significantly higher than those of the control group.

Table 6. Comparison of inflammatory factors and neurotrophic factors between the two groups of patients after treatment

Indicators	Treatment group (n = 45)	Control group (n = 45)	Mean difference (95% confidence interval)	t	*p*
hs-CRP (mg/L)	2.86±1.12	3.74±1.35	-0.88 (-1.40–0.36)	3.37	0.001
Hcy (μmol/L)	11.24±3.18	13.67±3.52	-2.43 (-3.83–1.03)	3.44	0.001
IL-6 (pg/mL)	4.83±1.76	6.12±2.04	-1.29 (-2.09–0.49)	3.19	0.002
BDNF (ng/mL)	24.37±4.85	20.56±4.61	3.81 (1.83-5.79)	3.82	< 0.001

Note: Hs-CRP is high-sensitivity C-reactive protein, Hcy is homocysteine, IL-6 is interleukin-6, BDNF is brain-derived neurotrophic factor. After treatment, the levels of inflammatory factors in the treatment group were significantly lower than those in the control group, while the level of BDNF was significantly higher than that in the control group.

Table 7. Multivariate logistic regression analysis of HBOT effects on clinical outcomes

Outcome indicators	β	SE	Wald χ^2	OR value (95% confidence interval)	*p*
A reduction of ≥ 20% in LDL-C	1.12	0.41	7.46	3.06 (1.37-6.84)	0.006
An increase of ≥ 3 points in the MoCA test	1.24	0.43	8.31	3.45 (1.49-8.02)	0.004
The hs-CRP level decreased by at least 30%	0.96	0.38	6.38	2.61 (1.24-5.50)	0.012
BDNF increases by ≥ 20%	1.08	0.40	7.29	2.94 (1.34-6.45)	0.007

Note: BDNF is brain-derived neurotrophic factor; the covariates include age, gender, baseline score, stroke type, and duration.

Cognitive function score

Table 5 shows that cognitive function improved significantly more in the treatment group than in the control group after treatment. The MoCA score of the treatment group (25.38 ± 2.14 points) was higher than that of the control group (22.96 ± 2.31 points), with a mean difference of 2.42 (95% CI 1.49-3.35), t = 5.16, $P < 0.001$; the MMSE score of the treatment group (27.14 ± 1.86 points) was also higher than that of the control group (25.08 ± 2.03 points), with a mean difference of 2.06 (95% CI 1.25-2.87), t = 5.03, $P < 0.001$.

Inflammatory factors and neurotrophic factors

After treatment, the inflammatory indicators in the treatment group were lower than in the control group (**Table 6**), whereas the neurotrophic factors were higher. The hs-CRP treatment group (2.86 ± 1.12 mg/L) was lower than the control group (3.74 ± 1.35 mg/L), with a mean difference of -0.88 (95% CI -1.40 to -0.36), t = 3.37, $P = 0.001$; the IL-6 treatment group (4.83 ± 1.76 pg/mL) was lower than the control group (6.12 ± 2.04 pg/mL), with a mean difference of -1.29 (95% CI -2.09 to -0.49), t = 3.19, $P = 0.002$; the BDNF treatment group (24.37 ± 4.85 ng/mL) was higher than the control group (20.56 ± 4.61 ng/mL), with a mean difference of 3.81 (95% CI 1.83 to 5.79), t = 3.82, $P < 0.001$.

Multivariate logistic regression analysis

Table 7 presents the analysis results of the multivariate Logistic regression model, aiming to evaluate the independent association between HBOT and the occurrence of clinically significant improvements in various outcome indicators. The adjusted confounding factors in the model include age, gender, baseline cognitive score (MoCA), baseline LDL-C level,

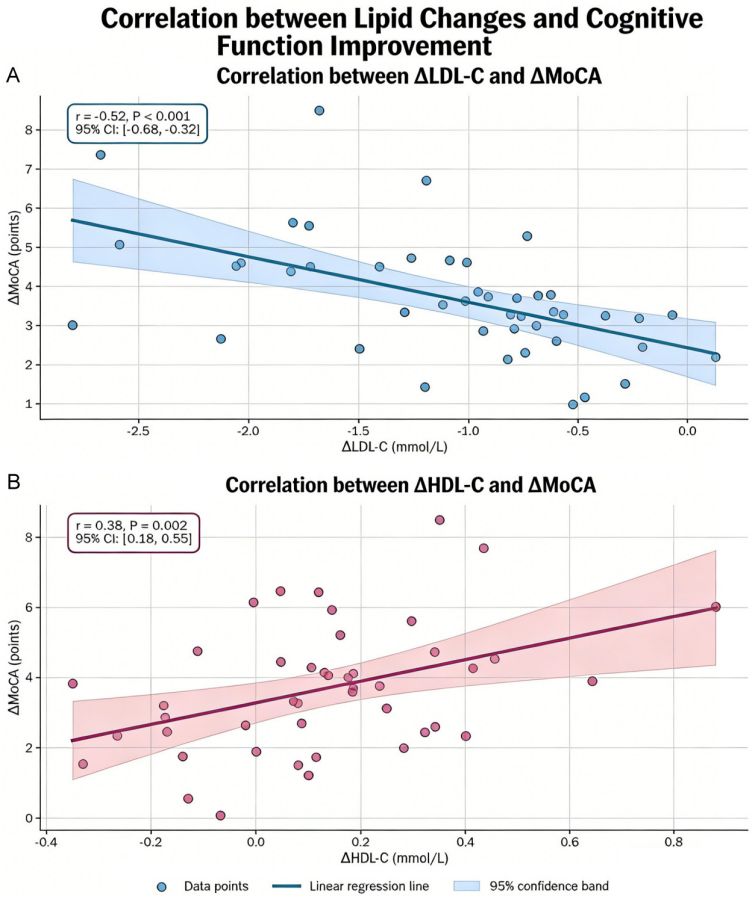

Figure 2. Scatter plots showing the correlation between changes in blood lipid levels and improvements in cognitive function. MoCA is the Montreal Cognitive Assessment Scale, LDL-C is low-density lipoprotein cholesterol, HDL-C is high-density lipoprotein cholesterol. A. The change in LDL-C (ΔLDL-C) was negatively correlated with the change in MoCA score (ΔMoCA) (r = -0.52, 95% CI -0.68 to -0.32, $P < 0.001$); B. The change in HDL-C (ΔHDL-C) was positively correlated with ΔMoCA (r = 0.38, 95% CI 0.18-0.55, $P = 0.002$). ΔLDL-C, ΔHDL-C, and ΔMoCA represent the changes from baseline to post-treatment. Solid lines represent linear regression fit lines, and shaded areas indicate 95% confidence intervals.

stroke type (ischemic or hemorrhagic), and disease duration. After adjusting for these confounding factors, HBOT was significantly associated with clinical improvements in multiple outcome indicators. For lipid indicators, the probability of achieving a ≥ 20% reduction in LDL-C in patients receiving HBOT was 3.06 times that of the control group (OR = 3.06, 95% CI 1.37-6.84, $P = 0.006$). For cognitive function, the probability of achieving a ≥ 3-point increase in MoCA score (considered the minimum clinically significant difference) in the HBOT group was 3.45 times that of the control group (OR = 3.45, 95% CI 1.49-8.02, $P = 0.004$). For inflammatory indicators, the probability of achieving a ≥ 30% reduction in hs-CRP in the HBOT group was 2.61 times that of the control group (OR = 2.61, 95% CI 1.24-5.50, $P = 0.012$). For neurotrophic status, the probability of achieving a ≥ 20% increase in BDNF in the HBOT group was 2.94 times that of the control group (OR = 2.94, 95% CI 1.34-6.45, $P = 0.007$). This indicates that even after considering potential confounding factors such as age, gender, and baseline severity of the disease, HBOT remains an independent protective factor for improving lipid profiles, restoring cognitive function, reducing inflammatory levels, and enhancing neurotrophic status in patients with PSCI. The OR values are all greater than 2.5, and the lower limits of the 95% confidence intervals are all greater than 1, suggesting that the clinical benefits brought by HBOT have a strong and robust effect size.

The correlation analysis revealed a significant association between lipid changes and improvements in cognitive function (**Figure 2**). As shown in **Figure 2A**, the reduction in LDL-C was moderately negatively correlated with the increase in MoCA score (r = -0.52, 95% CI -0.68 to -0.32, $P < 0.001$), meaning that the greater the decrease in LDL-C, the more significant the improvement in cognitive function. In contrast, as shown in **Figure 2B**, the increase in HDL-C was positively correlated with the increase in MoCA score (r = 0.38, 95% CI 0.18 to 0.55, $P = 0.002$). These correlations provided the prerequisite for the subsequent mediation effect analysis.

Generalized estimating equation analysis

The generalized estimating equation shows (**Table 8**) that there is a significant interaction

Table 8. Interaction effect of time and grouping on the primary outcome as analyzed by GEE

Indicators	Source	β	SE	Wald χ^2	*p*
LDL-C	Time	0.34	0.12	8.03	0.005
	Grouping	0.52	0.18	8.34	0.004
	Time × Group	0.41	0.15	7.47	0.006
MoCA	Time	0.47	0.14	11.27	0.001
	Grouping	0.63	0.21	9.00	0.003
	Time × Group	0.56	0.17	10.85	0.001

Note: MoCA is the Montreal Cognitive Assessment Scale, LDL-C is low-density lipoprotein cholesterol. The time × group interaction effect was significant, suggesting that the treatment group showed a more pronounced improvement trend during the follow-up period compared to the control group.

Table 9. Analysis of the mediating effect of lipid changes in the promotion of MoCA improvement by hyperbaric oxygen therapy

Mediating variable	Type of effect	Effect size	Boot SE	Boot 95% CI	Percentage of intermediaries (%)
ΔLDL-C	Overall effect	2.42	0.47	1.51-3.33	100.00
	Direct effect	1.91	0.46	1.09-2.73	78.93
	Indirect effect	0.51	0.18	0.16-0.87	21.07
ΔHDL-C	Overall effect	2.42	0.47	1.51-3.33	100.00
	Direct effect	2.15	0.45	1.27-3.03	88.84
	Indirect effect	0.27	0.14	0.02-0.58	11.16

Note: LDL-C is low-density lipoprotein cholesterol, HDL-C is high-density lipoprotein cholesterol. ΔMoCA represents the difference between the post-treatment MoCA score and the baseline value; ΔLDL-C and ΔHDL-C represent the differences from the baseline values after treatment; The Bootstrap method was used to randomly sample 1,000 times; If the 95% confidence interval of the indirect effect does not include 0, it indicates a significant mediating effect.

effect between time and group on the primary outcome. For LDL-C, the time × group interaction term was Wald χ^2 = 7.47, P = 0.006; for MoCA, the time × group interaction term was Wald χ^2 = 10.85, P = 0.001. This indicates that the treatment group showed a significantly faster decline in LDL-C and an increase in MoCA during the follow-up period compared to the control group, and the intervention effect accumulated and strengthened over time.

Mediation effect analysis

The mediation effect analysis further explored the potential mediating role of lipid changes in the cognitive improvement promoted by HBOT. Using the change value of LDL-C as the mediating variable, the results showed that the indirect effect was 0.51 (95% CI 0.16-0.87), with a mediation proportion of 21.07%, indicating that the reduction of LDL-C partially mediated the improvement effect of HBOT on the MoCA score. Using the change value of HDL-C as the mediating variable, the indirect effect was 0.27 (95% CI 0.02-0.58), with a mediation proportion of 11.16%, suggesting that the increase of HDL-C also exerted a partial mediating effect, but the effect intensity was lower than that of LDL-C. The above results are shown in **Table 9**.

The results of the sensitivity analysis

The sensitivity analysis verified the robustness of the main results (**Table 10**). The main analysis (after PSM) showed that the improvement in MoCA from baseline in the treatment group (4.00 ± 1.86 points) was significantly greater than that in the control group (1.63 ± 1.79 points), with a mean difference of 2.37 (95% CI 1.61-3.13), t = 6.18, *P* < 0.001. This between-group difference in the change score (ΔMoCA) is consistent with the post-treatment absolute scores presented in **Table 4**, where the treatment group also showed superior cognitive performance. After excluding those with poor compliance, the mean difference was 2.54 (95% CI 1.78-3.30), t = 6.63, *P* < 0.001; the mean difference in the unmatched full sample analysis was 2.35 (95% CI 1.64-3.06), t = 6.55,

Table 10. The results of the sensitivity analysis

Analysis strategy	Improvement (points) of MoCA in the treatment group	Improvement (points) of MoCA in the control group	Mean difference (95% confidence interval)	*p*
Main analysis (after PSM)	4.00±1.86	1.63±1.79	2.37 (1.61-3.13)	< 0.001
Exclude those with poor compliance	4.12±1.81	1.58±1.76	2.54 (1.78-3.30)	< 0.001
Not all samples matched	3.92±1.94	1.57±1.83	2.35 (1.64-3.06)	< 0.001
1:2 Match	4.03±1.88	1.71±1.85	2.32 (1.58-3.06)	< 0.001

Note: MoCA is the Montreal Cognitive Assessment Scale. Across different sensitivity analysis strategies, the direction and significance of group differences are consistent, indicating that the results are robust and reliable.

Table 11. Multivariate regression analysis of baseline BDNF levels and the degree of improvement in MoCA

Variable	Beta value	SE	Standardized β	t	*p*	95% CI
HBOT group	2.38	0.45	0.48	5.29	< 0.001	1.49-3.27
Baseline BDNF level	0.31	0.13	0.22	2.38	0.018	0.06-0.56
Baseline MoCA	0.12	0.09	0.13	1.33	0.186	-0.06-0.30
Age	-0.03	0.02	-0.12	1.50	0.137	-0.07-0.01
Male (referring to female)	0.28	0.38	0.07	0.74	0.462	-0.48-1.04

Note: HBOT is Hyperbaric oxygen therapy. BDNF is brain-derived neurotrophic factor. MoCA is the Montreal Cognitive Assessment Scale. Dependent variable: ΔMoCA (the difference between the post-treatment MoCA score and the baseline MoCA score); HBOT group assignment (treatment group = 1, control group = 0); covariates included age, gender, and baseline MoCA score; $R^2 = 0.342$, model F = 5.68, $P < 0.001$.

$P < 0.001$; the mean difference in the 1:2 matching analysis was 2.32 (95% CI 1.58-3.06), t = 6.22, $P < 0.001$; after multivariate correction, the mean difference was 2.28 (95% CI 1.52-3.04), $P < 0.001$. Across all sensitivity analysis strategies, the direction of differences between the groups was consistent, the effect sizes were similar, and the 95% confidence intervals overlapped, confirming that the research conclusion was robust and reliable.

Subgroup analysis

Based on the median baseline BDNF level of 18.9 ng/mL in the treatment group of 45 patients, the patients were divided into the high BDNF group (n = 22) and the low BDNF group (n = 23). There was no statistically significant difference in baseline MoCA scores between the two groups (21.45 ± 2.38 vs. 21.31 ± 2.45; t = 0.20, $P = 0.844$), and the groups were comparable. After treatment, the MoCA scores of both groups increased significantly compared with baseline (all $P < 0.001$). The improvement in MoCA scores in the high BDNF group was 4.43 ± 1.92 points, and in the low BDNF group was 3.52 ± 1.74 points. The difference between the groups was statistically significant (mean difference of 0.91 points, 95% CI 0.02 to 1.80, t = 2.07, P = 0.045), suggesting that patients with higher baseline BDNF levels showed greater cognitive improvement from HBOT.

Multivariate regression analysis (**Table 11**) further corrected for age, gender, and baseline MoCA score. The results showed that the baseline BDNF level was independently positively correlated with the degree of MoCA improvement (β = 0.31, 95% CI 0.06-0.56, $P = 0.018$), and the HBOT group was also significantly associated with MoCA improvement (β = 2.38, $P < 0.001$). The model's fit $R^2 = 0.342$, indicating that these variables could explain 34.2% of the total variance in MoCA improvement.

These results suggest that the baseline BDNF level is an independent predictor of HBOT efficacy. Patients with higher baseline BDNF levels in PSCI may achieve greater improvements in cognitive function from HBOT. This finding provides preliminary clues for the individualized application of HBOT and helps in screening potential beneficiaries in clinical practice. The above results are shown in **Table 12**.

Table 12. Subgroup analysis of the impact of baseline BDNF levels on the efficacy of hyperbaric oxygen therapy

Grouping	Number of examples (n)	Baseline MoCA (Score)	Post-treatment MoCA (score)	ΔMoCA (points)	Group comparison t-value	Group comparison *p* value
The high BDNF group (≥ 18.9 ng/mL)	22	21.45±2.38	25.88±2.06	4.43±1.92	10.82	< 0.001
The low BDNF group (< 18.9 ng/mL)	23	21.31±2.45	24.83±2.19	3.52±1.74	9.70	< 0.001
Inter-group comparison	-	t = 0.20, P = 0.844	t = 1.66, P = 0.104	t = 2.07, P = 0.045	-	-

Note: BDNF is brain-derived neurotrophic factor. The patients in the treatment group were divided into two groups based on the median baseline BDNF level of 18.9 ng/mL; ΔMoCA represents the difference between the post-treatment MoCA score and the baseline MoCA score; there was no statistically significant difference in the baseline MoCA scores between the high BDNF group and the low BDNF group (P = 0.844), and they were comparable.

Discussion

This study, through a retrospective cohort design, for the first time systematically revealed the synergistic improvement effect of HBOT on the lipid profile and cognitive function of patients with PSCI. Adding three months of HBOT intervention on top of conventional rehabilitation not only significantly decreased TC, TG, LDL-C, and ApoB levels but also increased HDL-C and ApoA1 levels. This improvement in lipid profile was accompanied by significant increases in the MoCA and MMSE scores. Mediation effect analysis showed that the reduction in LDL-C partially mediated the improvement of cognitive function by HBOT, with a mediation ratio of 21.07%, providing new clues for understanding the neuroprotective mechanism of HBOT.

The close association between dyslipidemia and PSCI has been widely recognized. The lipid-regulating effect observed in this study is highly consistent with previous basic research. Dong et al. [38] found that after continuous 10-day HBOT treatment in ApoE knockout mice, abnormal lipid profiles and cognitive function decline were simultaneously improved. The mechanism involved hippocampal neuron protection. Kudchodkar et al. confirmed that HBOT alleviates atherosclerosis by inducing antioxidant responses [39]. This study extends this finding to the PSCI population, demonstrating that 30 cumulative HBOT sessions at 2.0 ATA can reduce LDL-C by an average of 0.55 mmol/L and increase HDL-C by an average of 0.16 mmol/L, with clear clinical significance within the adjustment range.

In terms of cognitive function improvement, the MoCA score in the treatment group increased by 4.00 points from baseline, significantly higher than the 1.63-point increase in the control group (group difference: 2.37 points). Yang et al.'s prospective study of patients with PSCI showed that the cognitive score after HBOT treatment was significantly better than that of the conventional treatment group, and that the serum inflammatory factor profile exhibited an anti-inflammatory phenotype [40]. Hadanny et al.'s randomized controlled study on chronic stroke patients showed that cognitive improvement could still be achieved after HBOT treatment many years after disease onset, suggesting that the intervention time window of HBOT may be wider than that of traditional rehabilitation [41]. It may exert long-term effects by inducing neuroplasticity. Khairy [42] recently published a case report that further supported these mechanisms through imaging evidence: a stroke patient received 83 sessions of HBOT 15 months after stroke onset, and DTI showed an increase in fractional anisotropy of white matter fibers, and SPECT showed a 15.83% increase in blood flow perfusion in the motor cortex and 15.92% increase in the frontal lobe cortex. Although this study did not collect imaging data, the association between lipid profile improvement and improvement in cerebral blood flow perfusion has been confirmed by previous studies. Gottfried et al. [43] proposed that HBOT improves cognitive function by inducing neuroplasticity and angiogenesis. This study further reveals that lipid improvement may be one of the upstream events of enhanced neuroplasticity. The inflammatory response plays a central role in the pathogenesis of PSCI. This study found that the levels of hs-CRP, IL-6, and Hcy in the treatment group were significantly lower than those in the control group, whereas the BDNF level was significantly increased. Xin Chen et al. discovered, using a low-oxygen-induced cognitive impairment mouse model, that HBOT could upregu-

late the expression of oleic acid and MBOAT2, alter membrane lipid composition, and reduce neuronal ferroptosis. Chen et al. systematically summarized that HBOT exerts neuroprotective effects through multiple pathways, such as regulating mitochondrial function, inhibiting neuroinflammation, and promoting neurogenesis [44]. It has been noted that HBOT exerts neuroprotective effects through multiple pathways, including regulation of mitochondrial function, inhibition of neuroinflammation, and promotion of neurogenesis and angiogenesis. The results of this study are consistent with the literature and further support the hypothesis that HBOT improves cognitive function through anti-inflammatory and neurotrophic pathways. A case report published in SpringerLink further supported this through imaging evidence: 15 months after stroke, a patient who received 83 sessions of HBOT showed an increase in fractional anisotropy of white matter fibers on DTI, and an increase of 15.83% and 15.92% in blood perfusion of the motor cortex and frontal lobe cortex on SPECT, providing a structural-functional coupling basis for cognitive improvement [42].

The mediating effect was found to be that LDL-C reduction partially mediates the cognitive benefits of HBOT, with significant implications for the mechanism. The biological rationale is as follows: LDL-C is the core driver of atherosclerosis, and reducing its levels improves cerebral blood flow reserve; oxidized LDL-C has direct neurotoxicity; improving the lipid profile may enhance the integrity of the blood-brain barrier by alleviating vascular endothelial inflammation [45]. Boussi-Gross et al. previously proposed that HBOT improves cognitive function by inducing neural plasticity [46]. This study further reveals that improvements in lipid profiles may be one of the upstream events underlying enhanced neural plasticity. The mediating proportion of 21.07% indicates that approximately 79% of the effect is mediated by other mechanisms, consistent with previous studies emphasizing multiple mechanisms, such as angiogenesis, synaptic remodeling, and improved mitochondrial function. In this study, hyperbaric oxygen therapy (HBOT) reduced LDL-C by 15.94% and TG by 17.17%. The reduction rates of both were similar, but the clinical significance of LDL-C was more prominent. LDL-C is the main driving factor of atherosclerosis, and its reduction helps stabilize plaques, improve cerebral blood flow, and reduce the direct toxicity of oxidized LDL-C to neurons (Zhou et al., 2025). The reduction of TG may be more related to HBOT's improvement of tissue oxygen supply, reduction of insulin resistance, and inhibition of fat breakdown [47]. The molecular mechanism by which HBOT regulates lipid metabolism is not yet fully understood, but clues can be seen from existing basic research. Previous studies have shown that hyperbaric oxygen can inhibit hepatic triglyceride synthesis by activating the AMPK signaling pathway, while cholesterol metabolism is partially regulated by modulating hydroxymethylglutaryl-CoA reductase activity and LDL receptor expression. The complexity of this pathway may explain why the reduction rates of LDL-C and TG are not completely parallel. In addition, peroxisome proliferator-activated receptor gamma (PPARγ), a key nuclear receptor regulating lipid metabolism and inflammatory responses, has been shown in previous studies to alleviate lipid metabolism disorders and insulin resistance induced by a high-fat diet by activating the PPARγ signaling pathway [48]. Liver X receptor alpha (LXRα) is involved in the regulation of reverse cholesterol transport and HDL synthesis, and some researchers have observed in an atherosclerosis model that HBOT can upregulate LXRα expression and promote cholesterol excretion [49]. In previous studies, the relationship between LDL-C and improvements in cognitive function was clearer, which is why this study analyzed it as an intermediary variable. Therefore, although the reduction rates of both were similar, LDL-C's core position in neuroprotection makes it a key target for HBOT to regulate lipid metabolism. Although this study did not detect the above molecular markers, the improvement in the lipid profile (reduction in LDL-C and increase in HDL-C) was consistent with the activation of the AMPK, PPARγ, and LXRα pathways, suggesting that these signaling pathways may be important targets for HBOT to regulate lipid metabolism. Future research should combine molecular biology techniques to further explore the signaling pathways by which HBOT regulates lipid metabolism. This study found that baseline BDNF levels were positively correlated with the cognitive improvement effect of HBOT. This finding is consistent with previous research trends in neurorehabilitation. BDNF,

as a neurotrophic factor, has a baseline level that may reflect patients' neural plasticity reserve capacity. Mechanistically, HBOT promotes neuronal survival and synaptic plasticity by increasing tissue oxygen pressure, and this process may require sufficient BDNF as a substrate. Therefore, patients with higher baseline BDNF levels may have a better neural repair foundation and thus respond more strongly to HBOT. This finding provides preliminary clues for the individualized application of HBOT: by detecting baseline BDNF levels to screen potential beneficiaries, it helps improve the cost-benefit ratio of the treatment. Future studies need to verify the clinical value of BDNF as a predictive marker through larger prospective studies with larger sample sizes and explore its optimal cutoff value.

From a clinical transformation perspective, HBOT, as a non-invasive physical therapy, can provide additional cognitive benefits beyond conventional medications and rehabilitation training, and is of practical significance for the comprehensive management of PSCI. Currently, the treatment of PSCI mainly relies on cholinesterase inhibitors, memantine, and statins, but the therapeutic effects are often unsatisfactory. The unique value of HBOT lies in the physical increase of blood oxygen pressure: under a 2.0 ATA environment, the plasma dissolved oxygen content can increase by 7-12 times, and the oxygen diffusion distance expands from 30 μm at normal pressure to over 100 μm. This physical effect is difficult to replace with drugs [50]. The HBOT protocol adopted in this study is 2.0 ATA at 60 minutes per session, with a total of 30 sessions (3 courses, each consisting of 10 sessions). This protocol is based on the commonly used doses in previous studies on PSCI and post-stroke rehabilitation. However, there is currently no unified standard for the optimal number of treatments and the course schedule. Some studies have shown that the efficacy of HBOT may have a dose-effect relationship, but excessive treatment frequency may increase the burden on patients and the risk of adverse events. Although this study did not set up different treatment groups for comparison, from the results of the generalized estimation equation of the time-group interaction effect, the improvement in cognitive function of the treatment group showed a continuous upward trend over time, and no plateau was observed, suggesting that 30 treatments may not have reached the maximum efficacy. In the future, prospective randomized controlled trials with parallel groups at different treatment frequencies (e.g., 10, 20, or 30 times) can be conducted to determine the optimal dose and treatment schedule for HBOT in PSCI patients, aiming to achieve the best balance between efficacy and resource investment. At the methodological level of the study, this research balanced confounding factors between groups using PSM, confirmed the interaction effect between time and group using GEE, and verified the robustness of the results through sensitivity analysis. After matching, each group had 45 samples. Post hoc power analysis showed that for the primary outcome, the MoCA score, the power was 0.86.

This study does have several limitations: The retrospective design cannot completely eliminate unmeasured confounding factors. Although the E-value calculation shows that the association between unmeasured confounding factors and treatment and outcome needs an OR > 2.5 to overturn the conclusion; the single-center study limits the generalizability of the results; the follow-up period only covers the point at the end of treatment, and the long-term efficacy maintenance situation could not be observed; thus the causal inference of the mediation effect analysis still requires caution, and there may be a bidirectional relationship between lipid changes and cognitive improvement. The patients included in this study all had mild to moderate cognitive impairment (with baseline MoCA scores ranging from 18 to 25), and the degree of dyslipidemia was mainly mild to moderate (with an average baseline LDL-C of 3.45 mmol/L). Therefore, the conclusions of this study are mainly applicable to this population. For patients with severe cognitive impairment (MoCA < 18) or severe dyslipidemia (LDL-C > 4.9 mmol/L), the efficacy and safety of HBOT still need to be further verified. Additionally, this study excluded patients with severe heart failure, chronic obstructive pulmonary disease, and a history of mental illness, suggesting that such patients may not be able to tolerate HBOT or may have potential risks. In clinical practice, it is recommended to conduct rigorous screening for patients scheduled to receive HBOT, including an otolaryngological

consultation to assess eustachian tube function, cardiac function assessment, and baseline cognitive function evaluation, to ensure the safety and effectiveness of the treatment.

This study is placed within the existing evidence framework. Multiple systematic reviews have preliminarily confirmed the positive impact of HBOT on cognitive function. A systematic review by Mariana Cannellotto et al., which included multiple high-quality studies, supported the potential of HBOT to improve cognitive impairments caused by various etiologies [51]. Previous studies mostly focused on a single outcome measure and lacked multi-dimensional integrated analysis. This study constructed a more comprehensive effect spectrum by simultaneously detecting six lipid indicators, two cognitive scales, three inflammatory indicators, and one neurotrophic factor, and attempted to integrate indicators at different levels through mediation analysis. Future research should conduct multi-center randomized controlled trials to verify the causal relationship; extend the follow-up period to observe the persistence of therapeutic effects; combine functional magnetic resonance and positron emission tomography and other neuroimaging techniques to explore the patterns of brain structure and function remodeling induced by HBOT; conduct in-depth exploration of the molecular pathways by which HBOT regulates lipid metabolism based on metabolomics and lipidomics; and explore biomarkers that predict the efficacy of HBOT to promote individualized treatment decisions.

Limitations

This study has the following limitations: First, the retrospective design itself cannot completely eliminate the influence of unmeasured confounding factors. Although propensity score matching, multivariate regression, and sensitivity analysis were employed, selection and information biases may still persist. Secondly, as a single-center study, the sample size was relatively small, and the follow-up period only covered the end of treatment. Therefore, the long-term maintenance effects of hyperbaric oxygen therapy on cognitive function and lipid profile could not be observed. Thirdly, although the mediation effect analysis suggests that the reduction in LDL-C partially mediates the improvement in cognition, the mediation inference based on observational data should be interpreted with caution. There may be a bidirectional relationship or common upstream regulatory factors between lipid changes and cognitive improvement. Fourth, there is a lack of objective evidence at the imaging and molecular biology levels to support this. This study, based on correlations between lipid profiles and cognitive function, as well as an analysis of mediating effects, hypothesizes that hyperbaric oxygen therapy may indirectly protect the neurovascular unit by improving lipid metabolism. However, due to the limitations of the retrospective design, this study did not detect direct markers of blood-brain barrier integrity (such as the cerebrospinal fluid albumin-to-serum albumin ratio, tight junction proteins, etc.), and thus the above mechanistic inference lacks direct evidence. In the future, prospective studies combined with cerebrospinal fluid detection or neuroimaging techniques (such as dynamic contrast-enhanced magnetic resonance imaging) are needed to further verify the impact of hyperbaric oxygen therapy on the function of the blood-brain barrier, and the specific mechanisms by which it regulates lipid metabolism and neural plasticity still need to be further verified through in-depth basic research. Fifth, all the enrolled patients received statin therapy. Therefore, the research conclusion is mainly applicable to the population of post-stroke cognitive impairment (PSCI) patients who are currently receiving statin treatment. Since patients who did not use statins were not included in this study, it is impossible to separately evaluate the lipid regulation effect of hyperbaric oxygen therapy without the background of statin use, nor can it distinguish the synergistic or additive relationship between the lipid-lowering effect of hyperbaric oxygen therapy and statins. Future studies can be designed to include PSCI patients who did not use statins to more clearly evaluate the independent regulatory effect of hyperbaric oxygen therapy on lipid metabolism.

Conclusion

In conclusion, this study provides new evidence for the application of HBOT in the treatment of PSCI, confirming that it can significantly improve the lipid profile and promote cognitive recovery. Moreover, the improvement in lipid

levels partially mediates the cognitive benefits. This discovery incorporates lipid metabolism regulation into the explanation framework of the neuroprotective mechanism of HBOT, providing theoretical basis and practical references for optimizing the comprehensive intervention strategy for PSCI. In the complex process of post-stroke rehabilitation, HBOT, as a treatment method that acts on three targets - blood vessels, metabolism, and nerves simultaneously, deserves more attention and application in clinical practice.

Acknowledgements

This work was sponsored by Shanghai Municipal Health Commission, Clinical Research Special Project of the Health Industry (20234Y0100), the Scientific Research and Cultivation Fund of Jiangwan Hospital (JWKY2026-16), and the Teacher Professional Development Project (A1-0200-25-311007).

Disclosure of conflict of interest

None.

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References

[1] Ji Y, Wang X, Wu H, Ni X, Ren C, Wang T, Zhu H, Jiang Y and Zheng K. Incidence and risk factors of post-stroke cognitive impairment in convalescent elderly patients with first-episode acute ischemic stroke. Asian J Psychiatr 2023; 84: 103583.

[2] Kim HY, Back DB, Choi BR, Choi DH and Kwon KJ. Rodent models of post-stroke dementia. Int J Mol Sci 2022; 23: 10750.

[3] El Husseini N, Katzan IL, Rost NS, Blake ML, Byun E, Pendlebury ST, Aparicio HJ, Marquine MJ, Gottesman RF and Smith EE; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; Council on Hypertension; and Council on Lifestyle and Cardiometabolic Health. Cognitive impairment after ischemic and hemorrhagic stroke: a scientific statement from the American heart association/American stroke association. Stroke 2023; 54: e272-e291.

[4] Zhou W, Feng H, Tao H, Sun H, Zhang T, Wang Q and Zhang L. Factors influencing poststroke cognitive dysfunction: cross-sectional analysis. JMIR Form Res 2024; 8: e59572.

[5] Wang J, Yuan Y, Zhang Y, Liu H and Yan Y. Association between pre-stroke frailty status and post-stroke cognitive impairment in patients with acute large artery atherosclerotic cerebral infarction. Braz J Med Biol Res 2025; 58: e14837.

[6] Yu J and Wang J. Effect of post-stroke cognitive impairment and dementia on stroke recurrence and functional outcomes: a systematic review and meta-analysis. PLoS One 2024; 19: e0313633.

[7] Yuan M, Guo YS, Han Y, Gao ZK, Shen XY and Bi X. Effectiveness and mechanisms of enriched environment in post-stroke cognitive impairment. Behav Brain Res 2021; 410: 113357.

[8] Xie H, Zhang R, Cao S, Jiang J, Huang B, Liu M and Peng L. Repetitive transcranial magnetic stimulation in conjunction with scalp acupuncture in treating poststroke cognitive impairment: a protocol for systematic review and meta-analysis. BMJ Open 2025; 15: e098535.

[9] GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the global burden of disease study 2021. Lancet Neurol 2024; 23: 973-1003.

[10] Wang H, Wang J, Feng D, Wang L and Zhang J. Association between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and cognitive impairment in patients with acute mild ischemic stroke. Eur J Med Res 2025; 30: 430.

[11] Gao M, Huang L, Yi J, Zhang T, Zhu G, Zhang Q, Tian J, Zhao R, Duan X and Liu Z. The effectiveness of computerized cognitive training in patients with poststroke cognitive impairment: systematic review and meta-analysis. J Med Internet Res 2025; 27: e73140.

[12] Yang Y, Lu SR, Xu Q, Yu J, Wang Z, Zhang BS and Hong K. Predictive value of nutritional status and serological indicators in elderly patients with mild cognitive impairment. World J Psychiatry 2024; 14: 1925-1935.

[13] Thangaleela S, Ali A, Tandoro Y and Wang CK. Shared neuroinflammatory mechanisms across dementia types: an integrative review. Int J Mol Sci 2025; 27: 179.

[14] Jurcau A and Simion A. Cognition, statins, and cholesterol in elderly ischemic stroke patients: a neurologist's perspective. Medicina (Kaunas) 2021; 57: 616.

[15] Zhang H, Zhu W, Niu T, Wang Z, An K, Cao W, Shi J and Wang S. Inverted U-shaped correlation between serum low-density lipoprotein

cholesterol levels and cognitive functions of patients with type 2 diabetes mellitus. Lipids Health Dis 2021; 20: 103.
[16] Brunner A, Lindenmann J, Pistracher K, Micko A, Pichler A, Enzinger C, Smolle-Jüttner F, Wolfsberger S and Kurschel-Lackner S. Hyperbaric oxygen therapy for brain abscesses: a useful adjuvant treatment for a faster recovery. Neurosurg Rev 2025; 48: 583.
[17] Li X, Lu L, Min Y, Fu X, Guo K, Yang W, Li H, Xu H, Guo H and Huang Z. Efficacy and safety of hyperbaric oxygen therapy in acute ischaemic stroke: a systematic review and meta-analysis. BMC Neurol 2024; 24: 55.
[18] Meng Y, Zhou L, Xia Y, Jia C and Huang L. Breaking the hypoxia barrier: advances and challenges of hyperbaric oxygen therapy in cancer treatment. Biomed Pharmacother 2025; 193: 118703.
[19] Sakas R, Dan K, Edelman D, Abu-Ata S, Ben-Menashe A, Awad-Igbaria Y, Francois-Soustiel J and Palzur E. Hyperbaric oxygen therapy alleviates memory and motor impairments following traumatic brain injury via the modulation of mitochondrial-dysfunction-induced neuronal apoptosis in rats. Antioxidants (Basel) 2023; 12: 2034.
[20] Wang RY, Yang YR and Chang HC. The SDF1-CXCR4 axis is involved in the hyperbaric oxygen therapy-mediated neuronal cells migration in transient brain ischemic rats. Int J Mol Sci 2022; 23: 1780.
[21] Wu X, You J, Chen X, Zhou M, Ma H, Zhang T and Huang C. An overview of hyperbaric oxygen preconditioning against ischemic stroke. Metab Brain Dis 2023; 38: 855-872.
[22] Marcinkowska AB, Mankowska ND, Kot J and Winklewski PJ. Impact of hyperbaric oxygen therapy on cognitive functions: a systematic review. Neuropsychol Rev 2022; 32: 99-126.
[23] Liu H, Wang S, Wang J, Guo X, Song Y, Fu K, Gao Z, Liu D, He W and Yang LL. Energy metabolism in health and diseases. Signal Transduct Target Ther 2025; 10: 69.
[24] Huang C, Zhong Y, Yue C, He B, Li Y and Li J. The effect of hyperbaric oxygen therapy on the clinical outcomes of necrotizing soft tissue infections: a systematic review and meta-analysis. World J Emerg Surg 2023; 18: 23.
[25] Micun Z, Dobrzyńska W, Sieśkiewicz M, Zawadzka I, Dmuchowska DA, Wojewodzka-Zelezniakowicz M and Konopińska J. Hyperbaric oxygen therapy in ophthalmology: a narrative review. J Clin Med 2023; 13: 29.
[26] Saa JP, Tse T, Koh GCH, Yap P, Baum CM, Uribe-Rivera DE, Windecker SM, Ma H, Davis SM, Donnan GA and Carey LM. Characterization and individual-level prediction of cognitive state in the first year after 'mild' stroke. PLoS One 2024; 19: e0308103.
[27] Lim KB, Kim J, Lee HJ, Yoo J, You EC and Kang J. Correlation between montreal cognitive assessment and functional outcome in subacute stroke patients with cognitive dysfunction. Ann Rehabil Med 2018; 42: 26-34.
[28] Siotto M, Cocco C, Guerrini A, Bertoncini C, Germanotta M, Cipollini V, Cortellini L, Pavan A, Lattanzi S, Galluccio C, Insalaco S, Antonacci E, Ruco E and Aprile IG. Nutritional status in subacute post-stroke patients undergoing rehabilitation treatment: a protocol for a prospective observational study. BMC Sports Sci Med Rehabil 2025; 17: 138.
[29] Mertowska P, Mertowski S, Smolak K, Kita A, Kita G, Guz K, Pasiarski M and Grywalska E. Immune checkpoint pathway expression in lymphocyte subpopulations in patients with common variable immunodeficiency and chronic lymphocytic leukemia. Cancers (Basel) 2023; 15: 5184.
[30] Jurek A, Krzesiński P, Wierzbowski R, Uziębło-Życzkowska B, Witek P, Zieliński G, Kazimierczak A, Banak M and Gielerak G. The heart's function as a pump assessed via impedance cardiography and the autonomic system balance in patients with early-stage acromegaly. J Clin Med 2024; 13: 395.
[31] Chia GY, Yeo S, Ho JS, Jou E, Yeo LL and Tan BY. Neuroprotective agents in acute ischemic stroke. Explor Neuroprotective Ther 2023; 47-70.
[32] Li S, Wang X, Feng B, Li H and Wang Y. Loberamisal for Acute Ischaemic Stroke (LAIS): a multicentre, randomised, double-blind, parallel, placebo-controlled phase III clinical trial. Stroke Vasc Neurol 2025; 004582.
[33] Sharma RI, Mankowska ND, Marcinkowska AB, Winklewski PJ and Kot J. Critical flicker fusion frequency results during oxygen decompression in standard HBOT session - observational study. Int Marit Health 2024; 75: 167-176.
[34] Batenburg MCT, Maarse W, van der Leij F, Baas IO, Boonstra O, Lansdorp N, Doeksen A, van den Bongard DHJG and Verkooijen HM. The impact of hyperbaric oxygen therapy on late radiation toxicity and quality of life in breast cancer patients. Breast Cancer Res Treat 2021; 189: 425-433.
[35] Atri A, Dickerson BC, Clevenger C, Karlawish J, Knopman D, Lin PJ, Norman M, Onyike C, Sano M, Scanland S and Carrillo M. The alzheimer's association clinical practice guideline for the diagnostic evaluation, testing, counseling, and disclosure of suspected alzheimer's disease and related disorders (DETeCD-ADRD): validated clinical assessment instruments. Alzheimers Dement 2025; 21: e14335.

[36] Kaczmarek B, Ilkowska Z, Kropinska S, Tobis S, Krzyminska-Siemaszko R, Kaluzniak-Szymanowska A and Wieczorowska-Tobis K. Applying ACE-III, M-ACE and MMSE to diagnostic screening assessment of cognitive functions within the polish population. Int J Environ Res Public Health 2022; 19: 12257.
[37] de Jong FJM, Wingelaar TT and van Hulst RA. Pulmonary oxygen toxicity in occupational diving. Occup Med (Lond) 2023; 73: 231-232.
[38] Dong G, Liu Y, Liu H, Qiao C, Chen X and Wang L. Effect of hyperbaric oxygen treatment on lipid metabolism and neurovascular microenvironment in an apolipoprotein E knockout mouse model. J Integr Neurosci 2025; 24: 39656.
[39] Kudchodkar BJ, Pierce A and Dory L. Chronic hyperbaric oxygen treatment elicits an antioxidant response and attenuates atherosclerosis in apoE knockout mice. Atherosclerosis 2007; 193: 28-35.
[40] Yang X, Chen M, Shen Z, Rong T, Feng J, Wu M, Chen D and Wei Z. Linc00205/Mir-495-3p/Tnfsf15 axis is implicated in the treatment effect of hyperbaric oxygen therapy on patients with post-stroke cognitive impairment. Noro Psikiyatr Ars 2025; 62: 11-19.
[41] Hadanny A, Rittblat M, Bitterman M, May-Raz I, Suzin G, Boussi-Gross R, Zemel Y, Bechor Y, Catalogna M and Efrati S. Hyperbaric oxygen therapy improves neurocognitive functions of post-stroke patients - a retrospective analysis. Restor Neurol Neurosci 2020; 38: 93-107.
[42] Khairy S, Ginzarly M, Wang Z, Qureshi U, Zaitoun R and Efrati S. Anatomical and metabolic brain imaging correlation of neurological improvements following hyperbaric oxygen therapy-post-stroke recovery: a case report. J Med Case Rep 2025; 19: 493.
[43] Gottfried I, Schottlender N and Ashery U. Hyperbaric oxygen treatment-from mechanisms to cognitive improvement. Biomolecules 2021; 11: 1520.
[44] Chen X, Zhang J, Lin Y, Li Y, Wang H, Wang Z, Liu H, Hu Y and Liu L. Mechanism, prevention and treatment of cognitive impairment caused by high altitude exposure. Front Physiol 2023; 14: 1191058.
[45] Zou H, Zhang S, Cui X, Xu H, Zhou Z, Cheng D, Han Y, Tang Y, Dong A and Dong X. Advancements in the investigation of the mechanisms underlying cognitive aging. Biogerontology 2025; 26: 158.
[46] Doenyas-Barak K, Kutz I, Lang E, Assouline A, Hadanny A, Aberg KC, Levi G, Beberashvili I, Mayo A and Efrati S. Hyperbaric oxygen therapy for veterans with combat-associated posttraumatic stress disorder: a randomized, sham-controlled clinical trial. J Clin Psychiatry 2024; 85: 24m15464.
[47] Karaś R, Binduga UE, Januszewicz P and Szychowski KA. Review of hyperbaric oxygen therapy as an adjunctive intervention for metabolic disorders. Antioxidants (Basel) 2025; 14: 1443.
[48] Chen L, Xu S, Zhou Q, Zhao T, Zhao Y, Chen X, Zhu W, Ding J, Zheng H, Jiang M, Zhao S, Zhu H, Yang M and Wang F. HBOT alleviates diet-induced MASH by reprograming gut microbiota and liver metabolism in mice. Free Radic Biol Med 2025; 237: 600-614.
[49] Endo-Umeda K and Makishima M. Exploring the roles of liver X receptors in lipid metabolism and immunity in atherosclerosis. Biomolecules 2025; 15: 579.
[50] Liu W, Khatibi N, Sridharan A and Zhang JH. Application of medical gases in the field of neurobiology. Med Gas Res 2011; 1: 13.
[51] Cannellotto M, Yasells García A and Landa MS. Hyperoxia: effective mechanism of hyperbaric treatment at mild-pressure. Int J Mol Sci 2024; 25: 777.

Table S1. Comparison of baseline characteristics between patients with successful matching and those with unsuccessful matching

Indicators	Matched successful group (n = 90)	Unmatched groups (n = 25)	t/χ^2	*P*	SMD
Age (years)	63.95±7.76	66.21±8.34	2.03	0.045	0.28
Male [n (%)]	51 (56.67)	15 (60.00)	0.09	0.763	0.07
Years of education (years)	9.40±3.21	9.25±3.45	0.31	0.757	0.05
Ischemic stroke [n (%)]	69 (76.67)	18 (72.00)	0.23	0.631	0.11
Baseline MoCA (Score)	21.36±2.43	21.42±2.51	0.11	0.915	0.02
Baseline LDL-C (mmol/L)	3.44±0.88	3.82±0.95	2.06	0.042	0.42
Baseline TC (mmol/L)	5.40±1.11	5.47±1.23	0.38	0.702	0.06

Note: MoCA is the Montreal Cognitive Assessment Scale, MMSE is the Mini-Mental State Examination, LDL-C is low-density lipoprotein cholesterol, TC is total cholesterol, TG is Triglyceride, HDL-C is high-density lipoprotein cholesterol. SMD represents the standardized mean difference. The age and baseline LDL-C levels of the unmatched patients were significantly higher than those of the matched group, suggesting that caution should be exercised when extrapolating the conclusions of this study to the elderly and patients with severe hyperlipidemia.