

Hyperbaric oxygen therapy timing, early neurohemodynamic response and functional outcome in acute ischemic stroke

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Abstract. The optimal timing of HBOT initiation after AIS remains uncertain, particularly in relation to early cerebral hemodynamic responses and subsequent functional outcome. The present study determined whether hyperbaric oxygen therapy (HBOT) initiation timing was associated with early neurohemodynamic response and 90-day functional outcome among patients with acute ischemic stroke (AIS) who received HBOT within 72 h of symptom onset. In the present single-center, retrospective, exposure-stratified cohort study, patients were grouped according to HBOT initiation at <24 h, 24 to <48 h or 48 to 72 h following symptom onset. No non-HBOT comparator was included. The primary outcome was favorable functional status at 90 days, defined as a modified Rankin Scale (mRS) score of 0-2. Secondary analyses assessed early transcranial Doppler (TCD)-defined hemodynamic response, early neurological response, ordinal 90-day mRS shift, an exploratory treatment-emergent integrated early neurohemodynamic response phenotype and safety. Multivariable logistic regression, ordinal logistic regression and robustness analyses used the 48 to 72 h window as the reference. Among the 429 patients, HBOT initiation at <24 h (odds ratio (OR)=2.68; 95% CI, 1.55-4.63; $P<0.001$) and 24 to <48 h (OR=1.72; 95% CI, 1.04-2.82; $P=0.033$) was associated with greater odds of a favorable 90-day functional outcome than initiation at 48 to 72 h. Both earlier windows were also associated with greater odds of a lower 90-day mRS category (common OR=2.44; 95% CI, 1.53-3.88; $P<0.001$; common OR=1.68; 95% CI, 1.09-2.57; $P=0.017$). TCD hemodynamic response was more frequent in both earlier windows ($P<0.001$

and $P=0.043$), whereas a higher rate of early neurological response and a lower rate of early neurological deterioration were observed only in the <24 h window ($P=0.003$ and $P=0.025$, respectively). The exploratory integrated early neurohemodynamic response phenotype was associated with favorable functional outcome at 90 days (OR=2.95; 95% CI, 1.76-4.92; $P<0.001$). Safety outcomes did not differ significantly across initiation windows. Among HBOT-treated patients with AIS, earlier initiation was associated with more favorable early neurohemodynamic and neurological responses and improved 90-day functional outcomes, without evidence of increased safety events. As the present observational study included no non-HBOT comparator, the present findings do not establish HBOT efficacy relative to standard care without HBOT or a causal benefit of earlier initiation. Residual confounding and treatment-selection bias remain possible.

Introduction

Acute ischemic stroke (AIS) is a major cause of mortality and long-term disability worldwide. The global age-standardized incidence rate of ischemic stroke is projected to reach 89.32/100,000 population by 2030 (1). Early neurological recovery depends in part on restoration of cerebral perfusion, limitation of ischemic injury and prevention of early neurological deterioration (2,3). Although intravenous thrombolysis and endovascular thrombectomy have improved outcomes in patients who meet established time-window, imaging and clinical eligibility criteria, numerous patients remain ineligible because of delayed presentation, contraindications to intravenous thrombolysis, absence of a treatable large-vessel occlusion or unfavorable imaging or clinical profiles, and some continue to have residual hypoperfusion, microcirculatory dysfunction or incomplete neurological recovery despite standard acute management (4,5). Adjunctive strategies that can be integrated into routine stroke care and evaluated using accessible physiological markers therefore remain of clinical interest.

Hyperbaric oxygen therapy (HBOT) increases the amount of oxygen dissolved in plasma and may enhance oxygen delivery to ischemic or hypoperfused brain tissue under hyperbaric conditions (6,7). HBOT is used in some stroke centers equipped with hyperbaric chambers as an adjunct to standard stroke care in selected patients with AIS; however, the present

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study was not designed to assess efficacy relative to standard care without HBOT, and the optimal timing of initiation remains uncertain. Previous studies have focused primarily on associations between HBOT exposure and neurological or functional outcomes; few have examined whether the timing of HBOT initiation among treated patients is associated with early cerebrovascular physiological responses and subsequent functional outcome (8,9). Treatment timing is also shaped by access, workflow, baseline disease severity, clinical stability and feasibility, making careful consideration of pretreatment clinical, imaging and hemodynamic factors essential (10).

Transcranial Doppler (TCD) provides a non-invasive, repeatable method for assessing cerebral hemodynamics in patients with AIS (11,12). Middle cerebral artery mean flow velocity (MCA-MFV) reflects flow velocity, whereas the middle cerebral artery pulsatility index (MCA-PI) provides an index of downstream vascular resistance; changes in these parameters may therefore serve as accessible markers of early hemodynamic response (11,12). Early neurological response assessed with the National Institutes of Health Stroke Scale (NIHSS) captures short-term clinical change, whereas the modified Rankin Scale (mRS) remains the standard measure of 90-day functional outcome after stroke (13,14). Integrating early TCD and neurological responses may provide a structured description of treatment-emergent neurohemodynamic recovery without relying solely on delayed functional status.

Evidence linking HBOT initiation timing to early TCD-defined hemodynamic response, neurological recovery and 90-day functional outcome remains limited among patients with AIS who receive HBOT in routine clinical care (15,16). Safety is also relevant when considering earlier treatment, particularly with respect to symptomatic intracranial hemorrhage, barotrauma, treatment intolerance, oxygen-toxicity symptoms and other serious HBOT-related adverse events. The present study will therefore evaluate the association between the HBOT initiation window and early neurohemodynamic response, early neurological response, 90-day functional outcome and safety in a retrospective, exposure-stratified cohort in which all patients received HBOT. The present study will compare initiation windows within the HBOT-treated cohort and was not designed to estimate the efficacy of HBOT relative to standard care without HBOT.

Materials and methods

Study design and ethics. The present single-center, retrospective, exposure-stratified observational cohort was performed at Heyou Hospital (Foshan, China) and included hospitalized patients with AIS who received HBOT within 72 h of symptom onset. All treatment decisions, HBOT delivery, imaging, TCD assessments, neurological evaluations, safety monitoring and follow-up were derived from routine clinical records. The investigators neither assigned treatment nor modified clinical care. Consecutive eligible patients admitted between January 2022 and April 2025 were screened. The present study examined associations between the actual HBOT initiation window and early neurohemodynamic response, early neurological response, 90-day functional outcome and HBOT-related safety outcomes among patients treated with HBOT. No non-HBOT comparison group was included. The present study was

conducted in accordance with the Declaration of Helsinki and approved by the Heyou Hospital Institutional Review Board (approval no. 20250721-EXP1). As the analysis used de-identified retrospective data and involved no investigator-assigned intervention, the requirement for written informed consent was waived by the Heyou Hospital Institutional Review Board.

Study population. Eligible patients were 18–85 years of age, had AIS confirmed by cranial computed tomography (CT) or magnetic resonance (MR) imaging (17), were admitted within 72 h of symptom onset, had an anterior-circulation ischemic lesion and a baseline NIHSS score of 4–20, and received standard stroke care plus HBOT during hospitalization. Standard stroke care comprised routine guideline-based acute stroke management, including intravenous thrombolysis and/or endovascular thrombectomy when clinically indicated, as documented in the medical record. Eligibility also required a documented first HBOT initiation time within 72 h of symptom onset, baseline TCD before HBOT, repeat TCD within 72 h after the first HBOT session, baseline imaging sufficient to determine infarct side, Alberta Stroke Program Early CT Score (ASPECTS) (18), large vessel occlusion (LVO), and available 90-day mRS data (19). Exclusion criteria were pre-stroke mRS ≥ 3 , posterior-circulation stroke, transient ischemic attack (TIA), intracranial hemorrhage at admission, a neurological disorder that could interfere with functional assessment, baseline NIHSS < 4 or > 20 , HBOT initiated > 72 h after symptom onset, unavailable first-HBOT timing, missing baseline or early post-HBOT TCD data, missing 90-day mRS data, terminal disease with an expected survival of < 3 months or a 90-day functional outcome primarily determined by a non-stroke condition. Of the 1,627 hospitalized patients with AIS screened, 486 received HBOT within 72 h of symptom onset. A total of 429 patients met all eligibility criteria, comprising 136 patients in the < 24 h window, 161 in the 24 to < 48 h window and 132 in the 48 to 72 h window.

HBOT initiation window and treatment delivery. The primary exposure was the HBOT initiation window, defined by the interval from symptom onset to the start of compression for the first HBOT session. Symptom onset was determined from emergency records, stroke-pathway records, medical notes or family-provided history. When a definite symptom-onset time was documented, that time was used; when onset was unwitnessed or unknown, the last-known-well time, defined as the last time the patient was known to be free of symptoms attributable to the index stroke, was used. The first HBOT time was obtained from the HBOT treatment system or the first documented compression start time in the patients' medical records. Patients were classified into three initiation windows: < 24 h, 24 to < 48 h and 48–72 h. The 48–72 h window served as the reference in association models because it represented the latest initiation interval within the prespecified 72-h exposure range, allowing the two earlier windows to be compared with the latest-treated group. Onset-to-HBOT time was used to verify exposure separation, and onset-to-admission time was recorded as a timing-related clinical variable. The number of HBOT sessions completed within 10 days was used to characterize early treatment delivery across initiation windows. HBOT followed a standardized routine clinical protocol for

hospitalized patients with stroke: 2.0 atmospheres absolute (ATA), 100% oxygen for 60 min at therapeutic pressure once daily and 10-15 min each for compression and decompression, giving a total chamber time of 80-90 min per session. The planned course was 10 sessions over 10 days. Fewer sessions could be completed because of treatment interruption, clinical scheduling, discharge or other routine-care considerations; the actual number completed was analyzed as recorded. HBOT records were reviewed for chamber type, treatment pressure, compression, oxygen-breathing period, air-break arrangement, decompression, total session duration, daily frequency, number of sessions within 10 days, premature interruption and tolerance-related discontinuation. Pre-HBOT safety screening assessed cardiopulmonary stability, consciousness and cooperation, ear and sinus tolerance, and documented contraindications. Treatment interruption or cancellation was recorded when HBOT was stopped or withheld because of intolerance, ear or sinus symptoms, claustrophobia, suspected oxygen toxicity or other safety concerns. The present study compared initiation windows only among patients who received HBOT and did not compare HBOT with non-HBOT care.

Baseline clinical, imaging, laboratory and TCD variables.

Baseline data were extracted from electronic medical records, stroke evaluation records, imaging reports, laboratory systems, TCD reports, HBOT records, discharge summaries and follow-up documentation. Demographic and baseline functional variables included age, sex, body mass index (BMI) and pre-stroke mRS. Vascular risk factors and prior treatments included hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, coronary heart disease, previous stroke or TIA, current smoking and pre-stroke antithrombotic use. Acute stroke variables included baseline NIHSS score, systolic and diastolic blood pressure, Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype (20), infarct side, cortical involvement, baseline ASPECTS, LVO, baseline MCA stenosis or occlusion, intravenous thrombolysis and endovascular thrombectomy. MCA stenosis or occlusion was determined from available CT angiography, MR angiography and TCD records. Admission laboratory measures included white blood cell count, neutrophil-to-lymphocyte ratio (NLR), platelet count, glucose, D-dimer, fibrinogen, low-density lipoprotein cholesterol, serum creatinine, serum albumin and homocysteine. NLR was calculated from absolute neutrophil and lymphocyte counts measured in the same blood sample. Baseline TCD measures included affected side MCA-MFV, MCA-PI, MCA resistance index and the MCA-MFV asymmetry ratio (21), calculated as affected-side divided by contralateral MCA-MFV. Early post-HBOT TCD was performed within 72 h after the first HBOT session. Early MCA-MFV change was defined as the percentage change from baseline, whereas early MCA-PI change was defined as the absolute post-HBOT minus baseline difference.

Outcome definitions. The primary outcome was favorable functional status at 90 days, defined as an mRS score of 0-2. The 90-day mRS was also analyzed as an ordinal outcome ranging from 0 to 6. Early neurological response was defined as a decrease of ≥ 4 NIHSS points from baseline to day 7 or a

day-7 NIHSS score of 0-1. TCD hemodynamic response was defined as an increase of $\geq 20\%$ in affected-side MCA-MFV after HBOT without a concomitant increase in MCA-PI of ≥ 0.10 . The integrated early neurohemodynamic response phenotype required both TCD hemodynamic response and early neurological response. This phenotype was analyzed solely as an exploratory, post-treatment, treatment-emergent response marker; it was neither a baseline predictive factor nor a validated surrogate endpoint and was therefore not included as a covariate in the primary HBOT timing models. Early neurological deterioration was defined as an increase of ≥ 4 NIHSS points within 72 h after admission. Safety outcomes included symptomatic intracranial hemorrhage, 90-day mortality, middle ear barotrauma, sinus barotrauma or pressure symptoms, claustrophobia-related treatment interruption, oxygen-toxicity symptoms, severe HBOT-related adverse events and a composite safety endpoint. Symptomatic intracranial hemorrhage was defined as imaging-confirmed intracranial hemorrhage within 7 days accompanied by an increase of ≥ 4 NIHSS points. Middle ear barotrauma comprised documented ear pain or fullness, hearing decline, tympanic membrane congestion or retraction, bleeding or perforation during or after HBOT. Sinus barotrauma or pressure symptoms comprised documented sinus barotrauma, sinus pain or pressure symptoms during or after HBOT. Claustrophobia-related treatment interruption was defined as premature termination or cancellation of HBOT because of claustrophobia, marked anxiety or inability to tolerate the chamber. Oxygen-toxicity symptoms included suspected treatment-emergent manifestations such as seizure-like symptoms, visual disturbance, marked nausea or dizziness. A severe HBOT-related adverse event was defined as an event leading to premature termination of HBOT, specialist management, prolonged hospitalization or definite organ injury. The composite safety endpoint comprised symptomatic intracranial hemorrhage, 90-day mortality, 90-day recurrent stroke, middle ear barotrauma or a severe HBOT-related adverse event.

Data quality control and missing data handling. Data were extracted using a predefined case-report framework. Core exposure variables, HBOT delivery variables, TCD parameters, reperfusion therapy, NIHSS scores, mRS outcomes and safety events were cross-checked against source records. Imaging and TCD variables were reviewed using the prespecified operational definitions above and, where applicable, established published criteria for ASPECTS and TCD-based cerebrovascular assessment (11,12,18); discrepancies were resolved by re-examining the original records. Range and logical-consistency checks were applied to timing variables, clinical scores, laboratory values, TCD parameters, treatment records, safety records and follow-up outcomes. Values inconsistent with the expected sequence of symptom onset, admission, HBOT initiation, TCD assessment and outcome evaluation were verified against source records. Clinically plausible extreme values were retained after verification; unverifiable values were treated as missing. As the present study included all eligible patients during the present study period, no prospective sample-size calculation was performed. The final cohort comprised 429 patients. Admission glucose was missing in 4 patients; models including this variable

therefore used complete cases ($n=425$). Analyses not involving admission glucose retained the full cohort when applicable. No imputation was performed.

Statistical analysis. Continuous variables were summarized as mean $\pm$ SD or median (interquartile range), as appropriate, and categorical variables as n (%). Baseline characteristics and treatment-delivery variables were compared across HBOT initiation windows using one-way analysis of variance or the Kruskal-Wallis test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. No post hoc pairwise comparisons were performed for baseline or treatment-delivery variables; the reported P-values represent overall three-group tests. The primary association between HBOT initiation window and 90-day favorable functional outcome was estimated using multivariable logistic regression with the 48 to 72 h window as the reference. The main model adjusted for age, sex, pre-stroke mRS, baseline NIHSS score, hypertension, diabetes mellitus, atrial fibrillation, baseline ASPECTS, LVO, intravenous thrombolysis, endovascular thrombectomy, admission glucose, baseline affected-side MCA-MFV and baseline affected-side MCA-PI. The 90-day mRS shift was analyzed using ordinal logistic regression with the same covariates; common odds ratios (ORs) >1 indicate greater odds of a lower, more favorable mRS category. TCD hemodynamic response and early neurological response were analyzed using adjusted logistic models incorporating baseline stroke severity, reperfusion therapy, admission glucose and baseline TCD status. Due to the limited number of events, early neurological deterioration was analyzed using an exploratory parsimonious logistic model adjusted for baseline NIHSS score and ASPECTS and intravenous thrombolysis. The integrated early neurohemodynamic response phenotype was examined in an exploratory multivariable logistic model for 90-day favorable functional outcome adjusted for HBOT initiation window and baseline clinical and TCD covariates. Safety outcomes were compared across initiation windows using the χ^2 test or Fisher's exact test, as appropriate. Robustness analyses for the primary outcome included inverse probability of treatment weighting (IPTW) with stabilized multinomial propensity-score weights trimmed at the 1st and 99th percentiles. Additional analyses adjusted for onset-to-admission time or MCA-MFV asymmetry ratio excluded patients who underwent endovascular thrombectomy or received intravenous thrombolysis, and used mRS 0-1 as an alternative functional outcome. To address potential survivor/immortal-time-related selection, a 72-h landmark sensitivity analysis restricted the cohort to patients who were alive and clinically evaluable at 72 h after symptom onset and reassessed the primary association using the same covariate adjustment set. The IPTW model included the covariates used in the main adjusted model, and post-weighting balance was assessed using standardized mean differences (SMDs). Baseline covariate balance before and after weighting is summarized in Table SI. Prespecified exploratory subgroup analyses assessed the association between initiation at <24 h and 90-day favorable functional outcome, with heterogeneity tested using interaction terms. Additional post hoc subgroup analyses evaluated hypertension, diabetes mellitus and atrial fibrillation using the same framework. Incremental clinical utility was explored by comparing the baseline model with a

model that additionally included HBOT timing using the area under the receiver operating characteristic curve (AUC), integrated discrimination improvement (IDI) and decision curve analysis (DCA) (22). This analysis was not intended to develop a prediction model. Treatment-emergent variables, including TCD hemodynamic response, early neurological response and the integrated early neurohemodynamic response phenotype, were not included as covariates in the main HBOT timing models. All timing-model estimates were interpreted as associations rather than causal treatment effects. All tests were two-sided. Analyses were performed in R version 4.4.2 (Posit Software, PBC). $P<0.05$ was considered a statistically significant difference.

Results

Baseline characteristics across HBOT initiation windows. In the overall three-group comparison across the <24 h, 24- <48 h and 48 to 72 h initiation windows, baseline NIHSS score ($P=0.039$), admission glucose ($P=0.004$) and baseline affected-side MCA-PI ($P=0.029$) were higher, whereas baseline ASPECTS ($P=0.028$), intravenous thrombolysis use ($P<0.001$), baseline affected-side MCA-MFV ($P=0.044$) and MCA-MFV asymmetry ratio ($P=0.034$) were lower. NLR indicated a borderline between-group difference ($P=0.050$). No statistically significant differences were observed for age, BMI, sex, pre-stroke mRS, vascular risk factors, TOAST subtype, infarct side, cortical involvement, large vessel occlusion, baseline MCA stenosis or occlusion, endovascular thrombectomy or most laboratory measures (Table I).

Exposure separation and treatment delivery across HBOT initiation windows. Onset-to-HBOT and onset-to-admission times were longer across progressively later HBOT initiation windows (both $P<0.001$). The number of HBOT sessions completed within 10 days did not differ significantly across windows ($P=0.079$; Fig. 1A-C; Table SII); the median numbers were 9 (IQR, 8, 10), 9 (IQR, 8, 9) and 9 (IQR, 8, 9) for the <24 h, 24 to <48 h and 48 to 72 h groups, respectively.

Early neurohemodynamic and neurological responses across HBOT initiation windows. Earlier HBOT initiation was associated with a greater early increase in MCA-MFV and a smaller early change in MCA-PI (both $P<0.001$). Adjusted probabilities of TCD hemodynamic response ($P<0.001$) and early neurological response ($P=0.014$) were also higher with earlier initiation (Fig. 2).

Functional outcome distribution across HBOT initiation windows. The 90-day mRS distribution shifted toward less disability with earlier HBOT initiation ($P<0.001$). Relative to the 48 to 72 h window, initiation at <24 h was associated with greater odds of a lower 90-day mRS category (common OR=2.44; 95% CI, 1.53-3.88; $P<0.001$), as was initiation at 24 to <48 h (common OR=1.68; 95% CI, 1.09-2.57, $P=0.017$) (Fig. 3).

Adjusted associations of HBOT initiation windows with functional, hemodynamic and neurological outcomes. In adjusted models using the 48 to 72 h window as the reference,

Table I. Baseline and acute stroke characteristics according to HBOT initiation window.

Variable	<24 h (n=136)	24 to <48 h (n=161)	48 to 72 h (n=132)	Statistic	P-value
Age, years	64 (54, 74)	66 (56, 76)	68 (58, 78)	5.068	0.079
BMI, kg/m ²	24.6±3.5	24.0±3.3	23.8±3.3	2.087	0.125
Sex				0.205	0.902
Female	51 (37.5)	58 (36.0)	46 (34.8)		
Male	85 (62.5)	103 (64.0)	86 (65.2)		
Pre-stroke mRS				3.174	0.529
0	73 (53.7)	87 (54.0)	68 (51.5)		
1	42 (30.9)	56 (34.8)	51 (38.6)		
2	21 (15.4)	18 (11.2)	13 (9.8)		
Hypertension				2.431	0.297
No	48 (35.3)	58 (36.0)	37 (28.0)		
Yes	88 (64.7)	103 (64.0)	95 (72.0)		
Diabetes mellitus				1.861	0.394
No	101 (74.3)	113 (70.2)	88 (66.7)		
Yes	35 (25.7)	48 (29.8)	44 (33.3)		
Atrial fibrillation				1.121	0.571
No	105 (77.2)	125 (77.6)	96 (72.7)		
Yes	31 (22.8)	36 (22.4)	36 (27.3)		
Dyslipidemia				0.302	0.860
No	78 (57.4)	90 (55.9)	78 (59.1)		
Yes	58 (42.6)	71 (44.1)	54 (40.9)		
Coronary heart disease				4.212	0.122
No	105 (77.2)	135 (83.9)	114 (86.4)		
Yes	31 (22.8)	26 (16.1)	18 (13.6)		
Previous stroke or TIA				1.366	0.505
No	116 (85.3)	129 (80.1)	109 (82.6)		
Yes	20 (14.7)	32 (19.9)	23 (17.4)		
Current smoking				0.390	0.823
No	90 (66.2)	110 (68.3)	92 (69.7)		
Yes	46 (33.8)	51 (31.7)	40 (30.3)		
Pre-stroke antithrombotic use				4.604	0.100
No	104 (77.6)	126 (79.2)	91 (68.9)		
Yes	30 (22.4)	33 (20.8)	41 (31.1)		
Baseline NIHSS score	10 (7, 12)	10 (7, 13)	11 (8, 13)	6.509	0.039
Baseline systolic blood pressure, mmHg	149±22	152±22	155±22	1.820	0.163
Baseline diastolic blood pressure, mmHg	84 (74, 95)	86 (75, 96)	88 (77, 99)	3.922	0.141
Baseline ASPECTS	8 (7, 9)	8 (7, 9)	8 (7, 8)	7.137	0.028
TOAST subtype				10.687	0.220
Large-artery atherosclerosis	55 (40.4)	75 (46.6)	57 (43.2)		
Cardioembolism	26 (19.1)	34 (21.1)	32 (24.2)		
Small-vessel occlusion	34 (25.0)	26 (16.1)	17 (12.9)		
Other determined etiology	12 (8.8)	11 (6.8)	9 (6.8)		
Undetermined etiology	9 (6.6)	15 (9.3)	17 (12.9)		
Infarct side				6.917	0.140
Left	72 (52.9)	68 (42.2)	65 (49.2)		
Right	59 (43.4)	88 (54.7)	58 (43.9)		
Bilateral	5 (3.7)	5 (3.1)	9 (6.8)		
Cortical involvement				3.176	0.204
No	81 (59.6)	92 (57.1)	65 (49.2)		
Yes	55 (40.4)	69 (42.9)	67 (50.8)		

Table I. Continued.

Variable	<24 h (n=136)	24 to <48 h (n=161)	48 to 72 h (n=132)	Statistic	P-value
Large vessel occlusion				2.806	0.246
No	106 (77.9)	119 (73.9)	91 (68.9)		
Yes	30 (22.1)	42 (26.1)	41 (31.1)		
Baseline MCA stenosis or occlusion				3.429	0.180
No	97 (71.3)	106 (65.8)	80 (60.6)		
Yes	39 (28.7)	55 (34.2)	52 (39.4)		
Intravenous thrombolysis				28.607	<0.001
No	89 (65.4)	121 (75.2)	122 (92.4)		
Yes	47 (34.6)	40 (24.8)	10 (7.6)		
Endovascular thrombectomy				0.697	0.706
No	111 (81.6)	136 (84.5)	107 (81.1)		
Yes	25 (18.4)	25 (15.5)	25 (18.9)		
WBC, $\times 10^9/l$	7.9 $\pm$ 2.4	8.2 $\pm$ 2.5	8.5 $\pm$ 2.5	1.685	0.187
NLR	3.17 (1.23, 5.12)	3.60 (1.66, 5.54)	4.08 (2.13, 6.02)	6.001	0.050
Platelet count, $\times 10^9/l$	222 (156, 310)	212 (152, 272)	224 (146, 303)	1.383	0.501
Admission glucose, mmol/l	6.9 (4.9, 9.8)	7.7 (5.8, 10.4)	8.5 (6.2, 11.2)	11.204	0.004
D-dimer, mg/l	0.60 (0.16, 1.06)	0.70 (0.24, 1.15)	0.80 (0.35, 1.26)	4.836	0.089
Fibrinogen, g/l	3.5 $\pm$ 1.1	3.6 $\pm$ 1.1	3.7 $\pm$ 1.1	1.973	0.140
LDL-C, mmol/l	2.68 $\pm$ 0.87	2.76 $\pm$ 0.86	2.85 $\pm$ 0.85	1.271	0.282
Serum creatinine, μ mol/l	73.7 (53.6, 93.8)	76.6 (56.5, 96.7)	80.7 (60.6, 100.8)	3.431	0.180
Serum albumin, g/l	39.1 $\pm$ 5.3	38.4 $\pm$ 5.3	37.6 $\pm$ 5.3	2.639	0.073
Homocysteine, μ mol/l	13.9 (8.2, 19.6)	14.9 (9.2, 20.6)	16.1 (10.4, 21.8)	3.803	0.149
Baseline affected-side MCA-MFV, cm/s	47.9 $\pm$ 15.3	45.2 $\pm$ 15.2	43.3 $\pm$ 15.0	3.144	0.044
Baseline affected-side MCA-PI	1.02 (0.72, 1.31)	1.09 (0.79, 1.39)	1.17 (0.87, 1.46)	7.060	0.029
Baseline affected-side MCA-RI	0.61 (0.50, 0.72)	0.63 (0.52, 0.74)	0.65 (0.54, 0.76)	5.077	0.079
MCA-MFV asymmetry ratio	0.81 $\pm$ 0.20	0.78 $\pm$ 0.20	0.75 $\pm$ 0.20	3.416	0.034

Values are presented as mean $\pm$ SD, median (IQR), or n (%), according to variable type and distribution. Normality was assessed within each HBOT initiation window. Continuous variables were compared using one-way ANOVA or the Kruskal-Wallis test, as appropriate; categorical variables were compared using the χ^2 test or Fisher's exact test. ASPECTS, Alberta Stroke Program Early CT Score; BMI, body mass index; HBOT, hyperbaric oxygen therapy; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MCA-MFV, middle cerebral artery mean flow velocity; MCA-PI, middle cerebral artery pulsatility index; MCA-RI, middle cerebral artery resistance index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; TCD, transcranial Doppler; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WBC, white blood cell count.

initiation at <24 h and at 24 to <48 h was each associated with greater odds of a favorable 90-day functional outcome ($P<0.001$ and $P=0.033$, respectively), a lower 90-day mRS category ($P<0.001$ and $P=0.017$) and TCD hemodynamic response ($P<0.001$ and $P=0.043$). Initiation at <24 h was additionally associated with greater odds of early neurological response ($P=0.003$) and lower odds of early neurological deterioration ($P=0.025$). Neither association was significant for the 24 to <48 h window ($P=0.136$ and $P=0.162$, respectively; Table II).

Integrated early neurohemodynamic response phenotype and 90-day functional outcome. In the present exploratory analysis, the integrated early neurohemodynamic response phenotype was more frequent with earlier HBOT initiation ($P<0.001$). Favorable functional outcome at 90 days was also more frequent among phenotype-positive than

phenotype-negative patients ($P<0.001$). After adjustment for HBOT initiation window and baseline covariates, phenotype positivity remained associated with greater odds of favorable functional outcome (OR=2.95; 95% CI, 1.76-4.92; $P<0.001$) (Fig. 4). This treatment-emergent association was not interpreted as evidence that the phenotype is a baseline predictor or a validated surrogate endpoint.

Safety outcomes and robustness analyses across HBOT initiation windows. Safety outcomes did not differ significantly across HBOT initiation windows. Relative to the 48 to 72 h group, associations between earlier initiation and favorable 90-day functional outcome remained directionally consistent in the IPTW-weighted analysis, following additional adjustment for onset-to-admission time or MCA-MFV asymmetry ratio, after exclusion of patients who underwent endovascular thrombectomy or received intravenous thrombolysis, and

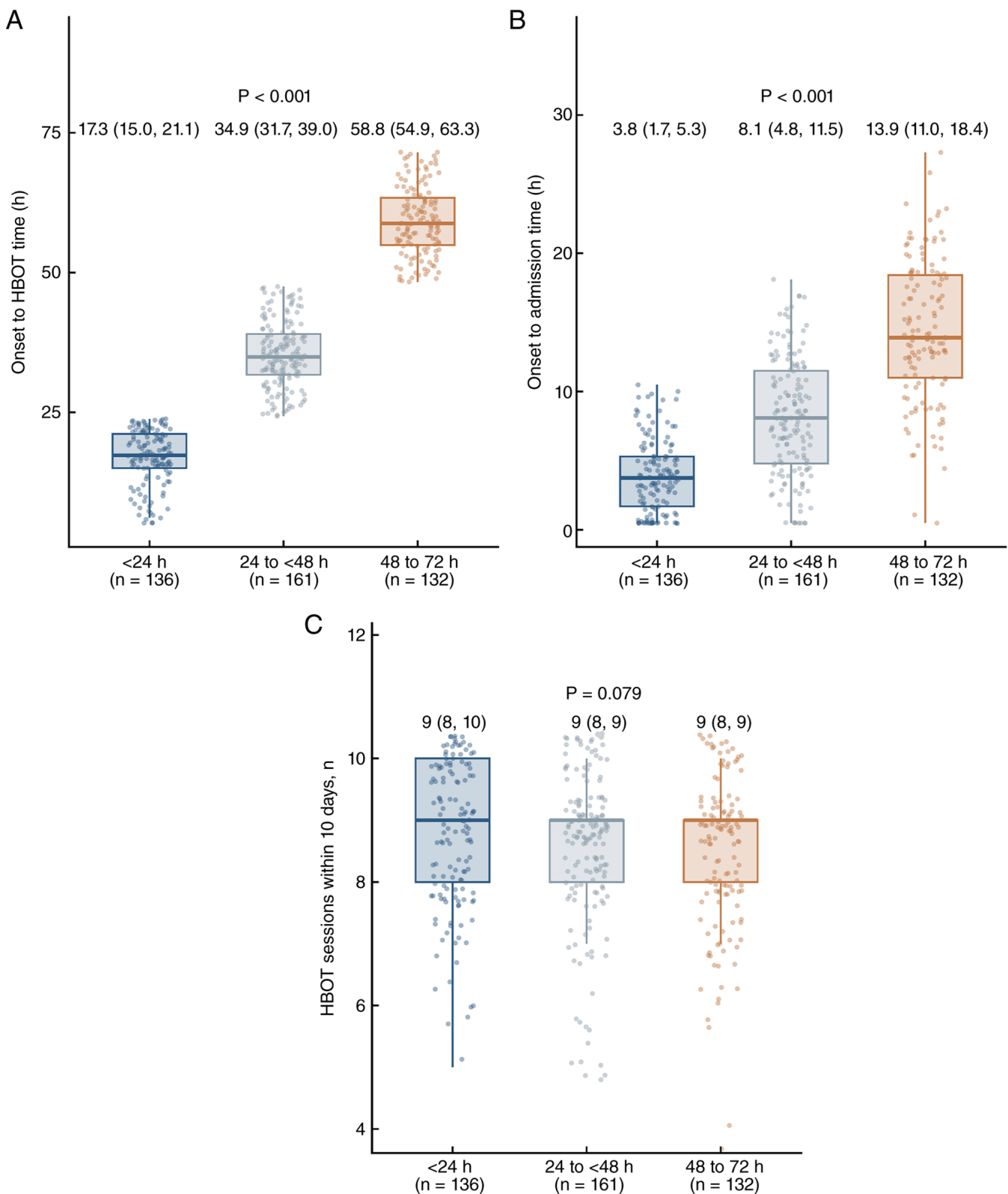


Figure 1. HBOT timing exposure and treatment delivery across initiation windows. (A) Onset-to-HBOT and (B) Onset-to-admission time across initiation windows. (C) Number of HBOT sessions completed within 10 days across initiation windows. HBOT, hyperbaric oxygen therapy.

when mRS 0-1 was used as the alternative outcome; these robustness analyses remained statistically significant. In the 72-h landmark analysis (n=421; 215 events), both the <24 h window (OR=2.51; 95% CI, 1.44-4.38; $P=0.001$) and the 24 to <48 h window (OR=1.76; 95% CI, 1.05-2.94; $P=0.031$)

remained associated with favorable functional outcome (Table III).

Supplementary analyses. After IPTW, covariate balance improved across the prespecified baseline clinical and TCD

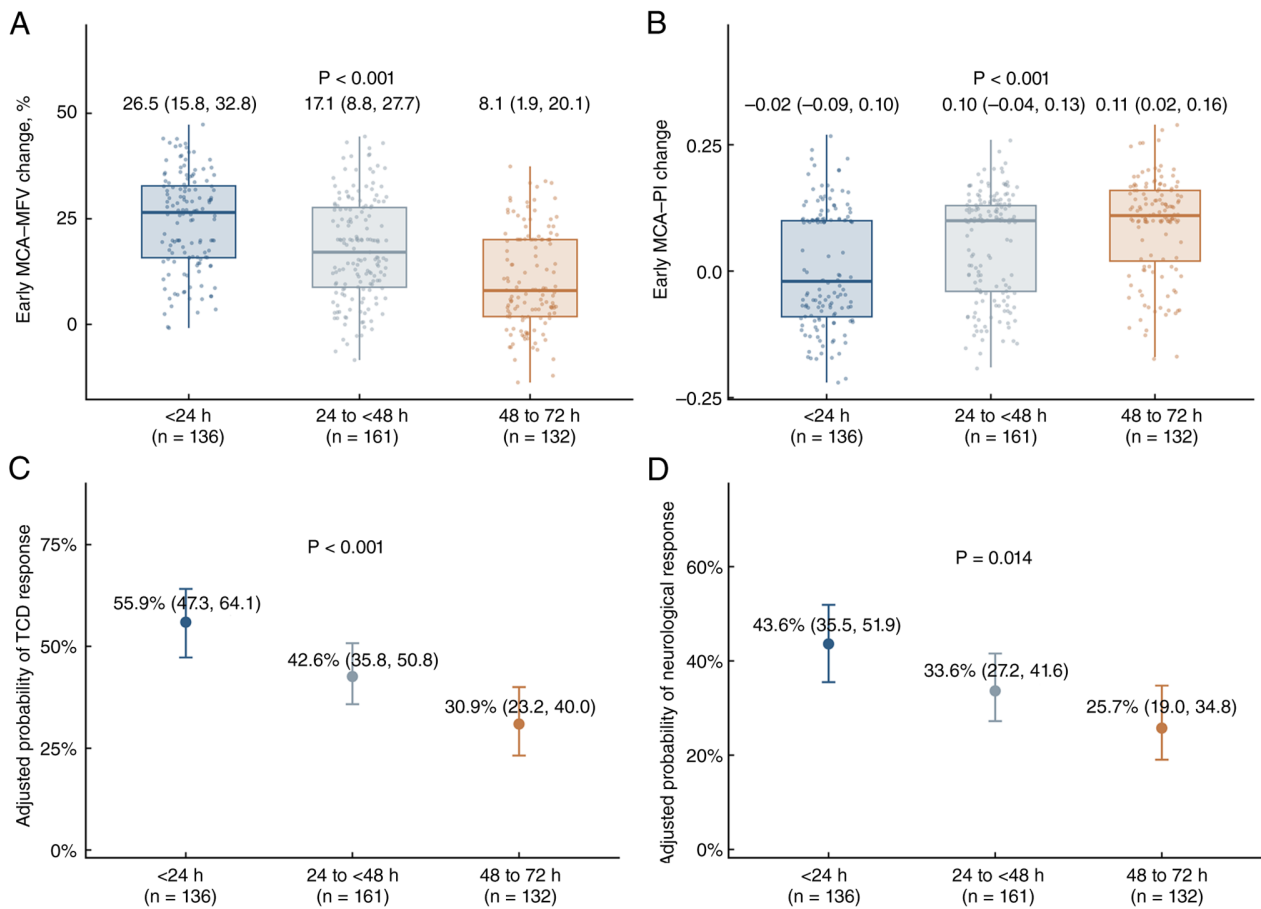


Figure 2. Early neurohemodynamic recovery pattern across hyperbaric oxygen therapy initiation windows. (A) Early change in MCA-MFV across initiation windows. (B) Early change in MCA-PI across initiation windows. (C) Adjusted probability of TCD hemodynamic response across initiation windows. (D) Adjusted probability of early neurological response across initiation windows. TCD, transcranial Doppler; MCA-MFV, middle cerebral artery-mean flow velocity; MCA-PI, middle cerebral artery pulsatility index.

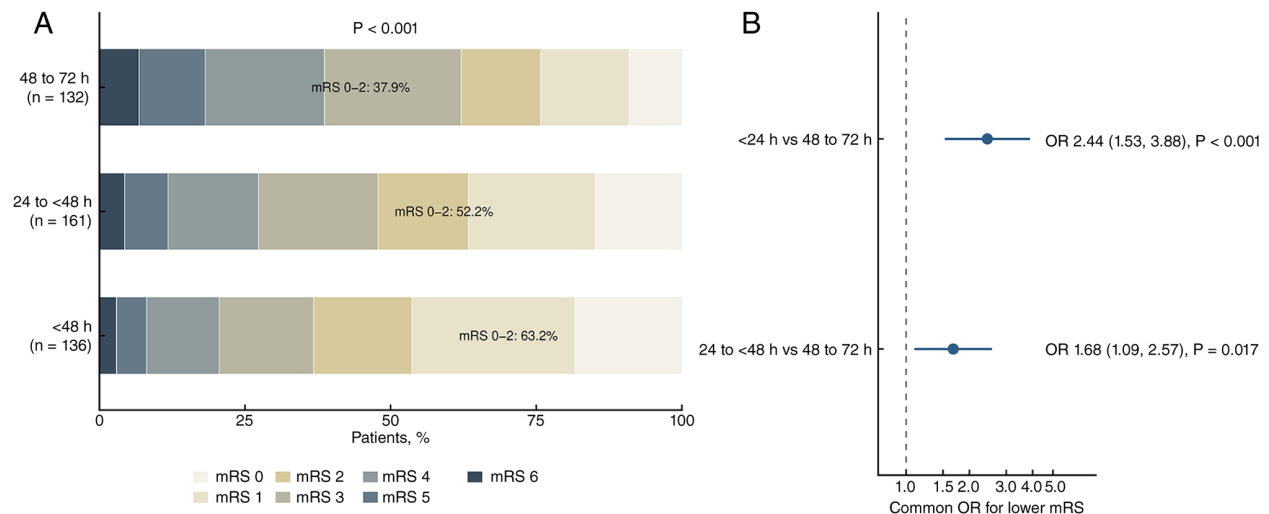


Figure 3. Functional outcome distribution across HBOT initiation windows. (A) Distribution of 90-day mRS categories across initiation windows. (B) Adjusted ordinal association between HBOT initiation window and a lower 90-day mRS category. mRS, modified Rankin Scale; OR, odds ratio; HBOT, hyperbaric oxygen therapy.

variables. All weighted covariates met the predefined balance threshold except baseline affected-side MCA-PI, for which the weighted SMD was 0.110, close to the conventional 0.10 threshold (Table SI).

In the prespecified exploratory subgroup analyses, the association between initiation at <24 h and favorable 90-day functional outcome was directionally consistent across most baseline strata. Baseline NIHSS score indicated evidence of interaction

Table II. Adjusted association models for functional, hemodynamic and neurological outcomes.

Outcome	Model	Adjustment strategy	N	Events	Comparison	Effect estimate	95% CI	P-value
90-day favorable functional outcome	Adjusted logistic regression	Clinical and baseline TCD augmented adjustment	425	217	<24 h vs. 48 to 72 h	2.68	1.55-4.63	<0.001
90-day favorable functional outcome	Adjusted logistic regression	Clinical and baseline TCD augmented adjustment	425	217	24 to <48 h vs. 48 to 72 h	1.72	1.04-2.82	0.033
90-day mRS shift	Ordinal logistic regression	Clinical and baseline TCD augmented adjustment	425	Ordinal outcome	<24 h vs. 48 to 72 h	2.44	1.53-3.88	<0.001
90-day mRS shift	Ordinal logistic regression	Clinical and baseline TCD augmented adjustment	425	Ordinal outcome	24 to <48 h vs. 48 to 72 h	1.68	1.09-2.57	0.017
TCD hemodynamic response	Adjusted logistic regression	Baseline severity, reperfusion, glucose and baseline TCD adjustment	425	184	<24 h vs. 48 to 72 h	2.93	1.70-5.06	<0.001
TCD hemodynamic response	Adjusted logistic regression	Baseline severity, reperfusion, glucose and baseline TCD adjustment	425	184	24 to <48 h vs. 48 to 72 h	1.68	1.02-2.79	0.043
Early neurological response	Adjusted logistic regression	Parsimonious clinical and baseline TCD adjustment	425	147	<24 h vs. 48 to 72 h	2.37	1.34-4.20	0.003
Early neurological response	Adjusted logistic regression	Parsimonious clinical and baseline TCD adjustment	425	147	24 to <48 h vs. 48 to 72 h	1.51	0.88-2.60	0.136
Early neurological deterioration	Exploratory parsimonious logistic regression	Parsimonious adjustment for baseline severity and thrombolysis	429	46	<24 h vs. 48 to 72 h	0.36	0.15-0.88	0.025
Early neurological deterioration	Exploratory parsimonious logistic regression	Parsimonious adjustment for baseline severity and thrombolysis	429	46	24 to <48 h vs. 48 to 72 h	0.60	0.30-1.22	0.162

Effect estimates are ORs for binary outcomes and common ORs for the ordinal 90-day mRS shift model; in the ordinal model, a common OR >1 indicates greater odds of a lower, more favorable mRS category. The reference group for all HBOT initiation-window comparisons was 48 to 72 h. The clinical and baseline TCD-augmented model included age, sex, pre-stroke mRS, baseline NIHSS score, hypertension, diabetes mellitus, atrial fibrillation, baseline ASPECTS, large vessel occlusion, intravenous thrombolysis, endovascular thrombectomy, admission glucose, baseline affected-side MCA-MFV and baseline affected-side MCA-PI. Models of TCD hemodynamic response and early neurological deterioration used the prespecified adjustment set comprising baseline severity, reperfusion therapy, admission glucose and baseline TCD status. Due to the limited number of events, early neurological deterioration was analyzed using an exploratory parsimonious model adjusted for baseline NIHSS score, baseline ASPECTS and intravenous thrombolysis. Models including admission glucose used complete cases. Post-treatment response variables were not included as covariates in the main exposure models. ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; EPV, events per variable; HBOT, hyperbaric oxygen therapy; MCA-MFV, middle cerebral artery mean flow velocity; MCA-PI, middle cerebral artery pulsatility index; mRS, modified Rankin Scale; OR, odds ratio; TCD, transcranial Doppler.

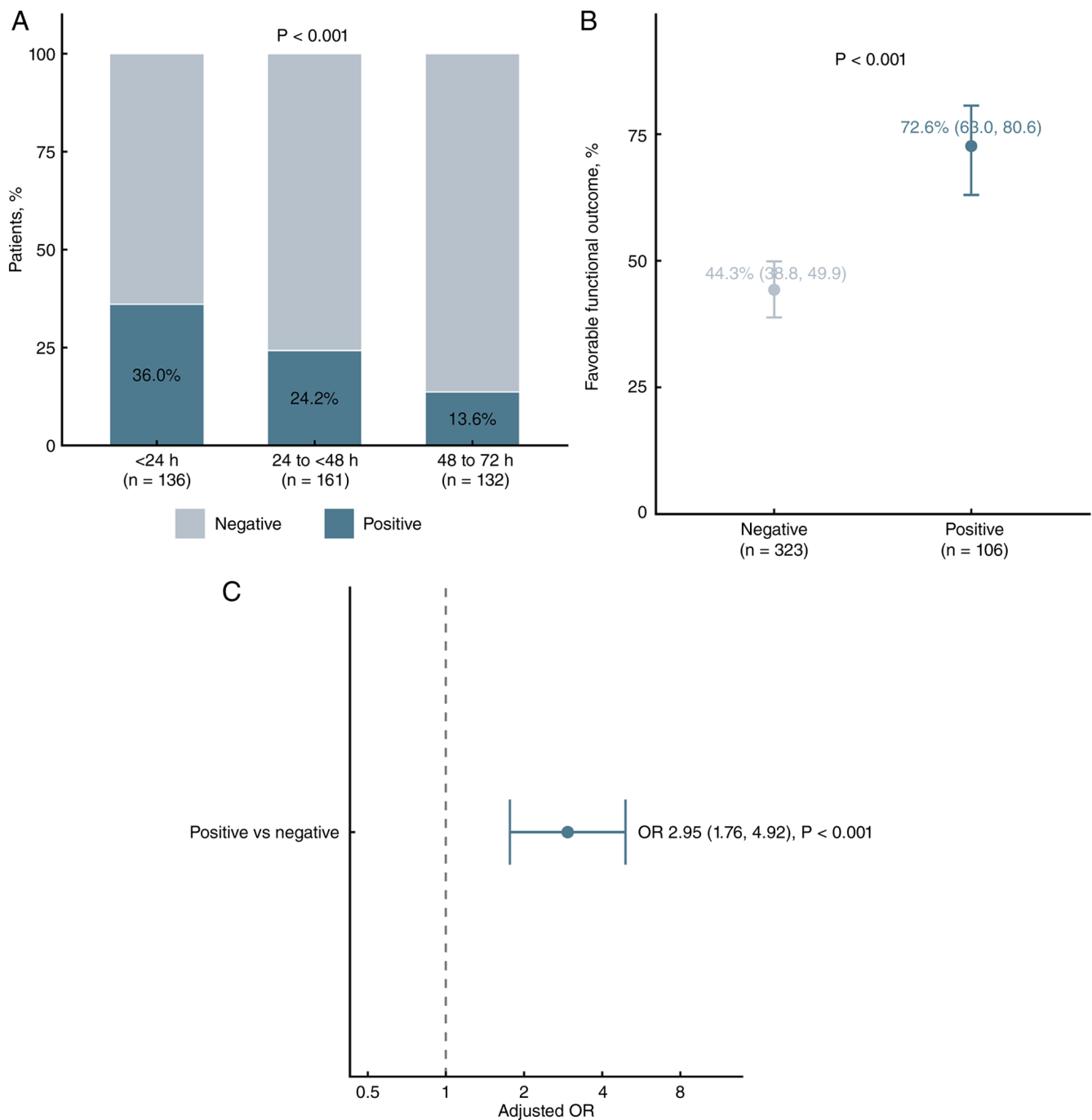


Figure 4. Exploratory integrated early neurohemodynamic response phenotype and 90-day favorable functional outcome. (A) Distribution of the exploratory treatment-emergent integrated early neurohemodynamic response phenotype across initiation windows. (B) Favorable 90-day functional outcome according to phenotype status. (C) adjusted association between phenotype positivity and favorable 90-day functional outcome. OR, odds ratio.

(interaction $P < 0.001$), whereas age, sex, baseline ASPECTS, LVO, intravenous thrombolysis, endovascular thrombectomy, admission glucose, baseline affected-side MCA-MFV and baseline affected-side MCA-PI did not show evidence of interaction (Fig. S1). Additional post hoc analyses across common comorbidities demonstrated the same overall direction. For <24 h versus 48 to 72 h, adjusted ORs were 2.71 (95% CI, 1.25-5.88) without hypertension and 2.66 (95% CI, 1.43-4.94) with hypertension; 2.74 (95% CI, 1.48-5.08) without diabetes mellitus and 2.53 (95% CI, 1.12-5.71) with diabetes mellitus; and 2.79 (95% CI, 1.51-5.15) without atrial fibrillation and 2.38 (95% CI, 1.02-5.54) with atrial fibrillation. No interaction was detected for hypertension

(interaction $P = 0.963$), diabetes mellitus (interaction $P = 0.861$) or atrial fibrillation (interaction $P = 0.734$; Fig. S1).

Adding HBOT timing to the baseline model increased the AUC numerically, although the change was not statistically significant ($P = 0.107$). IDI was higher after inclusion of HBOT timing ($P < 0.001$), and DCA suggested greater net benefit across part of the evaluated threshold-probability range (Fig. S2).

Discussion

In the present single-center retrospective cohort of HBOT-treated patients with AIS, earlier HBOT initiation was

Table III. Safety and robustness analyses of HBOT timing.

A, Safety outcomes						
Outcome or analysis	<24 h	24-<48 h	48-72 h	N	Events	Comparison Statistic/OR
Symptomatic intracranial hemorrhage	3 (2.2)	4 (2.5)	5 (3.8)			Exact
90-day mortality	4 (2.9)	7 (4.3)	9 (6.8)			2.323
Middle ear barotrauma	10 (7.4)	11 (6.8)	10 (7.6)			0.065
Sinus barotrauma or pressure symptoms	4 (2.9)	5 (3.1)	5 (3.8)			Exact
Claustrophobia-related treatment interruption	3 (2.2)	4 (2.5)	4 (3.0)			Exact
Oxygen toxicity symptoms	1 (0.7)	1 (0.6)	1 (0.8)			Exact
Severe HBOT-related adverse event	3 (2.2)	3 (1.9)	3 (2.3)			Exact
Composite safety endpoint	17 (12.5)	22 (13.7)	21 (15.9)			0.669
B, Robustness analyses						
Outcome or analysis	<24 h	24 to <48 h	48 to 72 h	N	Events	Comparison Statistic/OR
IPTW-weighted model				425	217	<24 h vs. 48 to 72 h 2.87
IPTW-weighted model				425	217	24 to <48 h vs. 48 to 72 h 2.02
Additional adjustment for onset-to-admission time				425	217	<24 h vs. 48 to 72 h 4.55
Additional adjustment for onset-to-admission time				425	217	24 to <48 h vs. 48 to 72 h 2.37
Additional adjustment for MCA-MFV asymmetry ratio				425	217	<24 h vs. 48 to 72 h 2.51
Additional adjustment for MCA-MFV asymmetry ratio				425	217	24 to <48 h vs. 48 to 72 h 1.66
Excluding endovascular thrombectomy				350	181	<24 h vs. 48 to 72 h 3.13
Excluding endovascular thrombectomy				350	181	24 to <48 h vs. 48 to 72 h 1.89
Excluding intravenous thrombolysis				328	161	<24 h vs. 48 to 72 h 2.57
Excluding intravenous thrombolysis				328	161	24 to <48 h vs. 48 to 72 h 1.74
72-h landmark analysis				421	215	<24 h vs. 48 to 72 h 2.51 (1.44-4.38; P=0.001)
72-h landmark analysis				421	215	24 to <48 h vs. 48 to 72 h 1.76 (1.05-2.94; P=0.031)
Alternative outcome: mRS 0-1				425	153	<24 h vs. 48 to 72 h 2.54
Alternative outcome: mRS 0-1				425	153	24 to <48 h vs. 48 to 72 h 1.75

Safety outcomes are presented as n (%). For safety outcomes, the Statistic/OR column gives the χ^2 statistic or 'Exact' when Fisher's exact test was used; for robustness analyses, the same column gives the OR. Robustness analyses evaluated the association between HBOT initiation window and favorable 90-day functional outcome, except for the alternative-outcome analysis using mRS 0-1. The 72-h landmark analysis was restricted to patients who were alive and clinically evaluable at 72 h after symptom onset; for these rows, the statistic/OR column reports the OR followed by the 95% CI and P-value in parentheses. The reference group for all HBOT initiation-window comparisons was 48 to 72 h. IPTW used stabilized multinomial propensity-score weights based on prespecified baseline clinical and TCD variables, with trimming at the 1st and 99th percentiles. The maximum weighted SMD after weighting was 0.110, indicating substantially improved covariate balance close to the conventional 0.10 threshold. Post-treatment response variables were not included as covariates in robustness models. CI, confidence interval; HBOT, hyperbaric oxygen therapy; IPTW, inverse probability of treatment weighting; MCA-MFV, middle cerebral artery mean flow velocity; mRS, modified Rankin Scale; OR, odds ratio; SMD, standardized mean difference; TCD, transcranial Doppler.

associated with a more favorable early neurohemodynamic profile, a higher frequency of early neurological response, lower 90-day disability and greater odds of favorable functional outcome. These associations persisted after adjustment for baseline clinical severity, imaging burden, reperfusion therapy, metabolic status and TCD measures, and remained directionally consistent across multiple robustness analyses, including the 72-h landmark analysis. Safety outcomes did not differ significantly across initiation windows. As treatment timing was not randomized and the groups differed in several baseline clinical, reperfusion, metabolic and TCD characteristics, these findings should be interpreted as timing-related associations within an HBOT-treated cohort, not as evidence that HBOT is superior to standard care without HBOT or that earlier initiation confers a causal benefit.

Recovery after AIS is shaped by residual perfusion, collateral flow, infarct burden and early change in neurological status, as reflected by serial NIHSS assessments. Previous studies have linked restoration or preservation of cerebral perfusion to subsequent neurological and functional recovery, although outcomes remain heterogeneous even after standard acute care (23-25). The present analysis adds a timing-focused perspective by examining patients who actually received HBOT and relating initiation timing to early TCD-derived physiological change and 90-day functional outcome. Notably, the earlier initiation groups had more favorable baseline profiles, including higher ASPECTS, greater use of intravenous thrombolysis, lower admission glucose, higher affected-side MCA-MFV and lower MCA-PI. These differences may reflect not only stroke biology but also symptom recognition, admission delay, treatment access, workflow efficiency, clinical stability and treatment feasibility. Multivariable adjustment, IPTW, landmark analysis and other sensitivity analyses reduce measured imbalance and some timing-related bias but cannot eliminate residual confounding or selection arising from unmeasured features of the clinical pathway.

The association between earlier HBOT initiation and a greater early increase in MCA-MFV is biologically plausible but does not establish a causal treatment effect. By increasing arterial and plasma oxygen content under pressure, HBOT may enhance oxygen availability in hypoperfused tissue when macrovascular reperfusion is incomplete or microcirculatory dysfunction persists (26,27). Earlier initiation was also associated with a more favorable TCD response and a smaller change in MCA-PI. These measures do not directly quantify tissue oxygenation or penumbral salvage; rather, they provide accessible physiological indicators that may capture early hemodynamic differences across initiation windows.

Prior studies of HBOT in ischemic stroke have yielded mixed findings, in part because of heterogeneity in patient selection, treatment timing, oxygen protocols, outcome definitions and study design (28,29). The majority have evaluated HBOT as a treatment category, whereas relatively few have examined initiation timing among patients who actually received therapy. The present study therefore addresses a narrower question: Within a HBOT-treated cohort, earlier initiation was associated with a more favorable early neurohemodynamic response following adjustment for several pretreatment clinical and TCD variables. This association remains susceptible to treatment-selection and

residual confounding despite a standardized planned HBOT protocol and multiple sensitivity analyses.

The integrated early neurohemodynamic response phenotype combined a physiological response signal with short-term neurological improvement. As it was defined after treatment, it was only analyzed as an exploratory, treatment-emergent marker. It was not a baseline predictor, did not determine HBOT timing and should not be regarded as a validated surrogate endpoint. TCD response alone may reflect altered flow velocity without corresponding clinical recovery, whereas NIHSS improvement may be influenced by baseline deficit pattern, infarct location or spontaneous recovery. Combining the two responses provides a clinically interpretable descriptive phenotype while remaining distinct from the delayed 90-day mRS outcome.

Phenotype positivity was more common in earlier initiation windows and was associated with greater odds of favorable 90-day functional outcome after adjustment for timing and baseline covariates. This association does not establish mediation, baseline prediction or surrogacy for the 90-day outcome. The phenotype is more appropriately viewed as an exploratory marker of early treatment-emergent response. This interpretation is consistent with evidence that early neurological improvement is associated with later functional status and that physiological measures can complement clinical scores (30,31). Its potential value lies in jointly characterizing early TCD and NIHSS responses in an observational HBOT-treated cohort; prospective validation is required before any predictive or surrogate role can be considered.

In the present study, earlier initiation windows were associated with a shift toward less disability across the full 90-day mRS distribution, consistent with the binary favorable-outcome analysis. This concordance is informative as dichotomizing the mRS can obscure clinically meaningful changes across disability levels. The agreement between ordinal and binary analyses therefore strengthens the internal consistency of the observed timing association.

The robustness analyses reduce but do not eliminate concerns about confounding and timing-related selection. IPTW substantially improved baseline covariate balance, although the maximum weighted SMD was 0.110, just above the conventional 0.10 threshold, owing to residual imbalance in baseline MCA-PI. The association remained directionally consistent after additional adjustment for onset-to-admission time or MCA-MFV asymmetry ratio, after exclusion of patients who underwent endovascular thrombectomy or received intravenous thrombolysis, and with mRS 0-1 as an alternative outcome. The 72-h landmark analysis produced similar estimates for both earlier initiation windows, reducing concern about survivor/immortal-time-related selection but not eliminating time-dependent selection in a retrospective treated cohort. These analyses are particularly notable because the timing groups differed in baseline severity, ASPECTS, reperfusion treatment, admission glucose and TCD parameters. Nevertheless, observational timing analyses remain vulnerable to residual confounding by treatment access, workflow, clinical stability and baseline severity. Consistency across analytic strategies supports the robustness of the association but does not imply causality (10).

Baseline NIHSS score indicated possible effect modification, although this finding is exploratory and should be interpreted cautiously because subgroup estimates from a single-center retrospective cohort can be unstable and multiple comparisons increase uncertainty. No clear interaction was detected across most other prespecified baseline variables. Additional post hoc analyses stratified by hypertension, diabetes mellitus and atrial fibrillation likewise demonstrated no significant interaction and preserved the overall direction of association. Larger multi-center studies with adequately powered, prespecified subgroup analyses are needed to determine whether timing associations vary by age, comorbidity burden, stroke severity, etiologic or vascular characteristics or reperfusion treatment.

Safety is central to the interpretation of earlier HBOT initiation in AIS, particularly with respect to hemorrhagic transformation, oxygen toxicity, barotrauma and treatment intolerance. In the present cohort, symptomatic intracranial hemorrhage and HBOT-related adverse events did not differ significantly across initiation windows. Middle ear barotrauma, the most directly relevant HBOT-specific safety outcome, occurred at similar frequencies across groups. No timing-related difference was observed for sinus pressure symptoms, claustrophobia-related interruption, oxygen-toxicity symptoms, severe HBOT-related adverse events or the composite safety endpoint.

These findings are broadly consistent with the HBOT safety literature, in which middle ear barotrauma is among the more common adverse events and serious oxygen-toxicity events are uncommon under monitored clinical protocols (32). However, the present data describe safety only among treated patients. They do not establish whether earlier HBOT is universally safe for all patients with AIS, because patients considered unsuitable for HBOT or unable to tolerate treatment may not have entered the treated cohort. This selection is key when considering clinical translation.

In the present study, adding HBOT timing to baseline variables produced a numerically higher AUC, but the increase was not statistically significant. IDI and DCA suggested some incremental prognostic utility, although these analyses were supplementary, were not designed to develop a prediction model and lacked external validation. The findings should therefore be interpreted as evidence that timing may add modest prognostic information beyond baseline factors, rather than as support for a clinically deployable prediction tool. This cautious interpretation is consistent with recommendations to consider discrimination, calibration and clinical utility jointly and to validate incremental performance metrics before clinical implementation (33,34).

Several limitations warrant emphasis. First, the present study was a single-center retrospective observational cohort in which treatment timing was not randomized. Residual confounding and treatment-selection bias may therefore persist despite multivariable adjustment, IPTW, landmark analysis and sensitivity analyses. Earlier initiation groups had several more favorable baseline characteristics, and unmeasured differences in clinical stability, access, workflow or clinician selection may have influenced both timing and outcome. Second, exposure was defined by the time of first HBOT; patients in later initiation windows necessarily had to remain alive and clinically eligible until treatment began,

creating potential survivor/immortal-time-related selection. The 72-h landmark analysis reduced, but could not eliminate, this concern. Third, because all included patients received HBOT within 72 h, the study cannot determine whether HBOT is superior to standard care without HBOT. Fourth, although planned HBOT pressure, oxygen concentration, therapeutic oxygen-breathing time, daily frequency and treatment course were standardized across groups, actual treatment exposure could vary because of interruption, scheduling, discharge or tolerance. The number of sessions completed within 10 days was similar across windows, but residual variation in delivered exposure remains possible. Fifth, TCD provides accessible bedside hemodynamic information but does not directly measure tissue oxygenation, infarct-core evolution, or penumbral salvage. Sixth, safety events were identified retrospectively from clinical records, and mild or transient symptoms may have been under-recorded. Finally, the integrated response phenotype, subgroup analyses and incremental utility analyses were exploratory and should be considered hypothesis-generating.

The findings should therefore be interpreted as associations among HBOT timing, early neurohemodynamic response and functional outcome within an HBOT-treated population. Prospective multicenter studies should use standardized, explicitly reported HBOT protocols; prespecified timing strategies that account for stroke severity and relevant clinical characteristics, and multimodal monitoring that integrates TCD, imaging and serial clinical assessment. Larger cohorts are also needed for prespecified subgroup analyses across age, comorbidity and stroke characteristics and for external validation of the exploratory integrated response phenotype. If a reproducible timing strategy is established prospectively, implementation should incorporate structured staff training to ensure consistent timing criteria, safety screening, HBOT delivery and multimodal monitoring. Such evidence is required before causal, protocol-level or implementation recommendations can be justified.

In the present retrospective, exposure-stratified cohort of HBOT-treated patients with AIS, earlier HBOT initiation was associated with more favorable early neurohemodynamic and neurological responses and improved 90-day functional outcomes. The exploratory treatment-emergent integrated response phenotype was also associated with favorable 90-day functional outcome after adjustment for HBOT timing and baseline covariates. Safety outcomes did not differ significantly across initiation windows. These findings do not establish HBOT efficacy relative to standard care without HBOT, a causal benefit of earlier initiation or a validated optimal timing strategy. Prospective multicenter studies using standardized HBOT protocols, multimodal monitoring and prespecified timing strategies are needed to confirm these observations.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XT, SS and QZ conceived and designed the present study. XT, SW, YW, GJ and CD collected the clinical data. XT and SS performed the statistical analysis. XT drafted the manuscript. QZ supervised the study and critically revised the manuscript. XT and QZ confirm the authenticity of all the raw data. XT, SS and SW contributed equally to this work. All authors read and approved the final version of the manuscript.

Ethical approval and consent to participate

The present study was approved by the Heyou Hospital Institutional Review Board (approval no. 20250721-EXP1). The requirement for written informed consent was waived by the Heyou Hospital Institutional Review Board as the retrospective study used de-identified clinical data and did not involve investigator-assigned intervention.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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