

Hyperbaric Oxygen Therapy and Visual Outcomes in Retinal Artery Occlusion: A Retrospective 24-Year Cohort Study

Elie Zaher

Rambam Health Care Campus

Lily Masalha

Rambam Health Care Campus

Wiessam Abu Ahmad

Hebrew University of Jerusalem

Gilad Allon

Meir Medical Center

Ivan Gur

Rambam Health Care Campus

Itzhak Beiran

Rambam Health Care Campus

Nitsan Duvdevan-Strier

duvden@technion.ac.il

Technion – Israel Institute of Technology

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Abstract

Purpose

To evaluate the association between hyperbaric oxygen therapy (HBOT) and visual outcomes in patients with acute non-arteritic retinal artery occlusion (RAO) managed according to a predefined institutional treatment protocol.

Methods

This retrospective cohort study included consecutive patients with central (CRAO) or branch retinal artery occlusion (BRAO) treated at a tertiary referral center between 2000 and 2023. Comparative analyses were restricted to protocol-consistent patients who met institutional HBOT eligibility criteria based on presentation within 8 hours of symptom onset. Visual outcomes were compared between HBOT-treated and standard-management groups. Multivariable linear regression was used to evaluate the association between HBOT and final visual acuity (VA) and change in VA (Δ VA) after adjustment for baseline clinical characteristics.

Results

The analytic cohort comprised 181 patients (125 CRAO and 56 BRAO), including 106 treated with HBOT and 75 managed without HBOT. Baseline VA was significantly worse in HBOT-treated patients. Final VA did not differ significantly between treatment groups in unadjusted analyses. However, HBOT-treated patients demonstrated greater visual improvement in both CRAO (Δ VA – 0.77 vs – 0.19 logMAR; $P = 0.007$) and BRAO (Δ VA – 0.76 vs – 0.07 logMAR; $P < 0.001$). After multivariable adjustment, HBOT remained independently associated with better final VA and greater visual improvement in both CRAO and BRAO.

Conclusion

In this retrospective protocol-based cohort, HBOT was independently associated with improved visual outcomes in patients with acute non-arteritic RAO despite poorer baseline vision. These findings support further prospective multicenter studies and randomized trials to clarify the therapeutic role of HBOT.

Key messages

What is known

- Hyperbaric oxygen therapy (HBOT) is a biologically plausible treatment for acute retinal artery occlusion (RAO), but evidence for its effectiveness remains limited and heterogeneous.

- Previous observational studies have reported inconsistent visual outcomes, and randomized evidence for acute RAO treatments remains limited.

What is new

- In a 24-year protocol-based cohort, HBOT was independently associated with better visual outcomes in both central and branch retinal artery occlusion after adjustment for baseline clinical characteristics.
- Greater visual improvement with HBOT was observed despite significantly poorer baseline visual acuity among treated patients.
- Restricting analyses to patients managed according to a predefined institutional HBOT eligibility protocol reduced treatment-allocation heterogeneity and strengthens the interpretation of this real-world observational study.

Introduction

Retinal artery occlusion (RAO), including central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO), is an acute ischemic retinal disorder that represents an ophthalmic emergency and is now recognized as a form of acute ischemic stroke.[1, 2] Patients with RAO are at increased risk of subsequent cerebrovascular events, cardiovascular morbidity, and mortality, highlighting the need for both urgent ophthalmic evaluation and systemic vascular assessment.[2–7] Visual prognosis remains poor, and experimental studies suggest that irreversible retinal injury develops rapidly after arterial occlusion, emphasizing the importance of timely intervention [1, 3, 8–10].

Although several treatments have been proposed for acute RAO, none has been established as standard therapy. [2, 11, 12] Conventional interventions, including ocular massage, anterior chamber paracentesis, and intraocular pressure-lowering therapies, have not demonstrated consistent benefit.[2, 11, 12] More recently, the phase III THEIA and TenCRAOS randomized trials failed to demonstrate statistically significant improvement in visual outcomes with thrombolytic therapy, highlighting the challenges of narrow treatment windows and treatment-related risks. [13, 14] Consequently, effective treatment for acute RAO remains an unmet clinical need.

Hyperbaric oxygen therapy (HBOT) has been proposed as an alternative treatment because increased dissolved plasma oxygen may diffuse from the choroidal circulation to the ischemic inner retina, maintaining retinal metabolism until spontaneous or therapeutic reperfusion occurs. [15–17] However, published evidence remains heterogeneous. Retrospective cohort studies have reported variable visual outcomes, and systematic reviews and meta-analyses have concluded that the certainty of available evidence is limited because of differences in study design, patient selection, treatment protocols, outcome measures, and treatment timing. [15–26]

We evaluated the association between HBOT and visual outcomes in patients with non-arteritic CRAO and BRAO treated at a tertiary referral center over a 24-year period. To improve comparability between

treatment groups, analyses were restricted to patients managed according to a predefined institutional HBOT eligibility protocol based on presentation within 8 hours of symptom onset. We then evaluated the association between HBOT and visual outcomes after adjustment for measured baseline clinical characteristics.

Methods

Study design

This retrospective cohort study included consecutive patients diagnosed with non-arteritic retinal artery occlusion (RAO) at Rambam Health Care Campus, a tertiary referral center in Haifa, Israel, between January 2000 and December 2023.

Compliance with Ethical Standards

The study was approved by the Institutional Review Board of Rambam Health Care Campus (approval no. RMB-D-0298-23), which waived the requirement for informed consent because of the retrospective design. All procedures were conducted in accordance with the Declaration of Helsinki. The study is reported in accordance with the STROBE guidelines for observational studies.

Study population

Patients with a confirmed diagnosis of central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) were eligible for inclusion. Patients were excluded if they had arteritic RAO, isolated cilioretinal artery occlusion, alternative diagnoses that could account for acute vision loss (including anterior ischemic optic neuropathy or retinal vasculitis), unavailable baseline or final visual acuity (VA), or missing documentation of symptom onset time.

Because HBOT eligibility at our institution was determined primarily by time from symptom onset, additional exclusions were applied to improve comparability between treatment groups. Patients who presented within 8 hours but did not receive HBOT despite meeting institutional eligibility criteria, and patients who underwent HBOT despite presenting more than 8 hours after symptom onset, were excluded from the comparative analyses. These restrictions were prespecified to minimize heterogeneity in treatment allocation and to reduce bias arising from inconsistent application of the institutional treatment protocol.

Clinical data collection

Electronic medical records were reviewed for demographic, systemic, ophthalmic, treatment, and outcome variables. Recorded variables included demographic, systemic, ophthalmic, treatment, and outcome characteristics, specifically age, sex, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, atrial fibrillation, previous cerebrovascular accident, obesity, anticoagulant treatment, RAO subtype, presence of a cherry-red spot (CRS) as documented in the ophthalmologist's examination,

acute treatments administered before HBOT, time from symptom onset to emergency department presentation, baseline VA, and final VA at the last available follow-up visit. Missingness was minimal for most variables but higher for cherry-red spot status and acute interventions before HBOT, particularly among HBOT-treated BRAO patients (see Results and Limitations).

For prognostic analyses within the HBOT-treated CRAO subgroup, presentation time was categorized as ≤ 4.5 hours or 4.5–8 hours according to clinically relevant treatment intervals derived from contemporary acute reperfusion studies.[13, 14]

Hyperbaric oxygen therapy

During the study period, patients presenting within 8 hours of symptom onset and without contraindications to HBOT were considered eligible for treatment according to the institutional management protocol, which was based on previous clinical experience at our center.[28] Patients presenting after 8 hours were generally managed without HBOT because treatment beyond this interval was not considered part of routine institutional practice.

HBOT was administered at 2.0–2.8 atmospheres absolute (ATA). Patients received three treatment sessions during the first 24 hours, usually separated by 4–6 hours. Additional sessions were prescribed according to the treating physician's assessment of visual response and clinical course. The institutional treatment protocol has been described previously.[29]

Visual acuity assessment

VA measurements obtained during routine clinical care were converted from Snellen notation to logarithm of the minimum angle of resolution (logMAR) values for statistical analyses. Visual acuity levels below Snellen chart limits, including counting fingers, hand motion, light perception, and no light perception, were converted using previously published conversion values.[31]

The visual outcome measures were final visual acuity (VA) at the last follow-up visit and change in visual acuity (Δ VA), calculated as final minus baseline logMAR values. In the logMAR scale, lower values represent better visual acuity; therefore, more negative Δ VA values indicate greater visual improvement. Additional outcomes included the proportion of patients achieving at least three lines of visual improvement (Δ VA ≤ -0.3 logMAR) and the proportion achieving a final VA of ≤ 0.3 logMAR (20/40 Snellen equivalent).

Safety assessment

Safety analyses included all patients who underwent HBOT, irrespective of eligibility for the comparative efficacy analyses. Medical records were reviewed for documented treatment-related adverse events, including symptoms suggestive of central nervous system oxygen toxicity, seizures, transient neurological symptoms, ear or sinus barotrauma, confinement anxiety, and otoscopic abnormalities. Middle ear barotrauma was classified according to the modified Teed classification.[32]

Statistical analysis

Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean $\pm$ standard deviation (SD), whereas categorical variables are summarized as frequencies and percentages. Distributional assumptions were evaluated by visual inspection of histograms and quantile–quantile plots. Two-sided P values <0.05 were considered statistically significant. Continuous variables were compared using Welch's t-test or the Mann–Whitney U test, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test. Because CRAO and BRAO differ in clinical presentation and prognosis, all comparative analyses were performed separately for each disease subtype. Associations between baseline characteristics and visual outcomes were initially explored using univariable linear regression. Variables with $P \leq 0.20$ in univariable analyses were considered candidates for multivariable modelling. HBOT treatment was retained in all multivariable models irrespective of statistical significance because it represented the primary exposure of interest. CRS was not included in multivariable models because it is closely associated with both presentation time and treatment allocation, creating the potential for multicollinearity. Separate multivariable linear regression models were constructed for final VA and Δ VA. Model estimates are reported as regression coefficients (β) with corresponding 95% confidence intervals (CI). No imputation of missing data was performed. Patients with missing data for visual outcome variables or treatment eligibility were excluded during cohort selection, whereas missing values for other variables were handled by complete-case analysis within the relevant statistical models. A prespecified exploratory analysis was performed among HBOT-treated patients with CRAO to identify factors associated with treatment response. Candidate predictors included age, baseline VA, hypertension, atrial fibrillation, previous cerebrovascular accident, and presentation within ≤ 4.5 hours versus 4.5–8 hours after symptom onset.

Results

Study cohort

A total of 322 patients with a diagnosis of RAO were identified during the study period. Ninety-one patients were excluded, including 25 with alternative diagnoses (3 giant cell arteritis, 2 anterior ischemic optic neuropathy, 6 occlusive vasculitis, and 14 other diagnoses), 3 with isolated cilioretinal artery occlusion, and 63 with unavailable baseline or final visual acuity (VA). An additional 50 patients were excluded from the comparative analyses because time from symptom onset was unavailable ($n = 14$) or treatment status was inconsistent with the institutional HBOT eligibility protocol ($n = 36$). Protocol-discordant treatment included 12 CRAO and 4 BRAO patients who received HBOT despite presenting >8 hours after symptom onset, and 13 CRAO and 7 BRAO patients who did not receive HBOT despite presenting within the institutional 8-hour treatment window. The final analytic cohort comprised 181 patients, including 125 with central retinal artery occlusion (CRAO) and 56 with branch retinal artery occlusion (BRAO), of whom 106 (58.6%) received hyperbaric oxygen therapy (HBOT) and 75 (41.4%) received standard management (Fig. 1).

Baseline characteristics

Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of Patients with CRAO and BRAO According to HBOT Treatment Status. Percentages were calculated using available data. Missing data were minimal for most baseline variables (0–2.9%). Higher missingness was observed for cherry-red spot status (up to 10.0%).

Variable	CRAO HBOT (n=90)	CRAO No HBOT (n=35)	P value	BRAO HBOT (n=16)	BRAO No HBOT (n=40)	P value
Demographics						
Age, years, mean $\pm$ SD	68.31 $\pm$ 14.70	70.09 $\pm$ 11.35	0.658	67.44 $\pm$ 17.96	65.33 $\pm$ 18.65	0.717
Male sex, n (%)	52 (57.8%)	16 (45.7%)	0.224	7 (43.8%)	22 (55.0%)	0.447
Vascular risk factors						
Hypertension, n (%)	55 (62.5%)	22 (64.7%)	0.821	11 (68.8%)	20 (51.3%)	0.235
Diabetes mellitus, n (%)	23 (26.1%)	15 (44.1%)	0.054	1 (6.2%)	8 (20.5%)	0.258
Hyperlipidemia, n (%)	27 (30.7%)	8 (23.5%)	0.434	4 (25.0%)	17 (43.6%)	0.197
Ischemic heart disease, n (%)	22 (25.0%)	8 (23.5%)	0.705	2 (12.5%)	10 (25.6%)	0.474
Atrial fibrillation, n (%)	8 (9.1%)	0 (0.0%)	0.104	5 (31.2%)	3 (7.7%)	0.038
Prior cerebrovascular accident, n (%)	8 (9.1%)	2 (5.9%)	0.724	1 (6.2%)	2 (5.1%)	1.000
Obesity, n (%)	4 (4.5%)	1 (2.9%)	1.000	0 (0.0%)	6 (15.4%)	0.165
Previous anticoagulation therapy, n (%)	42 (46.7%)	12 (34.3%)	0.210	6 (37.5%)	22 (55.0%)	0.237
Ophthalmic characteristics						
Baseline VA (logMAR), mean $\pm$ SD	2.39 $\pm$ 0.40	1.89 $\pm$ 0.80	<0.001	1.30 $\pm$ 1.10	0.46 $\pm$ 0.63	0.002
Cherry-red spot present, n (%)	29 (35.8%)	26 (76.5%)	<0.001	6 (40.0%)	4 (11.1%)	0.047

Abbreviations: AF, atrial fibrillation; VA, visual acuity; BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; CVA, cerebrovascular accident; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation

Age, sex, and most systemic vascular risk factors were comparable between treatment groups within both disease subtypes. Baseline VA was significantly worse among HBOT-treated patients than untreated patients in both the CRAO (2.39 ± 0.40 vs 1.89 ± 0.80 logMAR, $P < 0.001$) and BRAO (1.30 ± 1.10 vs 0.46 ± 0.63 logMAR, $P = 0.002$) subgroups.

Among patients with CRAO, a cherry-red spot was observed more frequently in untreated patients (76.5% vs 35.8%, $P < 0.001$), whereas in BRAO it was more common among HBOT-treated patients (40.0% vs 11.1%, $P = 0.047$). Among patients with available documentation, conservative acute interventions before HBOT were more commonly recorded in HBOT-treated patients than in untreated patients in both disease subgroups (Table 2).

Table 2. Acute interventions in Patients with CRAO and BRAO According to HBOT Treatment Status. Percentages were calculated using available data.

	CRAO HBOT (n=81)	CRAO No HBOT (n=33)	P value	BRAO HBOT (n=10)	BRAO No HBOT (n=39)	P value
Any prior treatment, n (%)	62 (76.5%)	7(21.2%)	<0.001	8 (80.0%)	8 (20.5%)	<0.001
Paracentesis, n (%)	35 (43.2%)	3(9.1%)	<0.001	0 (0.0%)	1 (2.6%)	1.000
Ocular massage, n (%)	45 (55.6%)	7 (21.2%)	<0.001	8 (80.0%)	6 (15.4%)	<0.001
Intraocular pressure-lowering medication, n (%)	43 (53.1%)	7 (21.2%)	0.002	8 (80.0%)	7 (17.9%)	<0.001
Systemic thrombolysis (tPA), n (%)	0 (0.0%)	0 (0.0%)	—	0 (0.0%)	0 (0.0%)	—
Rebreathing therapy, n (%)	8 (9.9%)	4 (12.1%)	0.742	3 (30.0%)	5 (12.8%)	0.333

Abbreviations: CRAO, central retinal artery occlusion; BRAO, branch retinal artery occlusion; HBOT, hyperbaric oxygen therapy; IOP, intraocular pressure; SD, standard deviation; tPA, tissue plasminogen activator.

Documentation of acute conservative interventions before HBOT was incomplete for a subset of patients, reflecting inconsistent recording in the medical record rather than a structured exclusion: missing in 9/90 (10.0%) of CRAO-HBOT, 2/35 (5.7%) of CRAO no HBOT, 6/16 (37.5%) of BRAO-HBOT, and

1/40 (2.5%) of BRAO no HBOT patients. Percentages in the table are calculated among patients with available documentation.

Documentation of these interventions was incomplete for a subset of patients, particularly among BRAO patients treated with HBOT (missing in 37.5%), and these comparisons should be interpreted with caution. No patients received tissue plasminogen activator.

Visual outcomes

Visual outcomes are summarized in Table 3 and adjusted treatment effects are presented in Figure 2.

Table 3. Visual Outcomes According to HBOT Treatment Status

	CRAO HBOT (n=90)	CRAO No HBOT (n=35)	P- value	BRAO HBOT (n=16)	BRAO No HBOT (n=40)	P- value
Final VA (logMAR), mean ± SD	1.62 ± 1.03	1.70 ± 0.90	0.865	0.54 ± 0.82	0.38 ± 0.58	0.300
ΔVA* (final – baseline logMAR), mean ± SD*	–0.77 ± 1.01	–0.19 ± 0.60	0.007	–0.76 ± 0.95	–0.07 ± 0.31	<0.001
Final VA ≤0.3 logMAR, n (%)	23 (25.6%)	6 (17.1%)	0.317	11 (68.8%)	27 (67.5%)	0.928
≥3-line visual improvement, n (%)	50 (55.6%)	9 (25.7%)	0.003	9 (56.2%)	2 (5.0%)	<0.001

Abbreviations: VA, visual acuity; BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation; ΔVA, change in visual acuity

*ΔVA was calculated as final minus baseline logMAR values; negative values indicate visual improvement.

Final VA did not differ significantly between HBOT-treated and untreated patients in either the CRAO (1.62 ± 1.03 vs 1.70 ± 0.90 logMAR, $P = 0.865$) or BRAO (0.54 ± 0.82 vs 0.38 ± 0.58 logMAR, $P = 0.300$) subgroup.

In contrast, HBOT-treated patients demonstrated significantly greater visual improvement (ΔVA) than untreated patients in both disease subgroups. In the CRAO subgroup, mean ΔVA was –0.77 ± 1.01 logMAR in HBOT-treated patients compared with –0.19 ± 0.60 logMAR in untreated patients ($P = 0.007$). Similarly, in the BRAO subgroup, mean ΔVA was –0.76 ± 0.95 versus –0.07 ± 0.31 logMAR ($P < 0.001$).

The proportion of patients achieving at least three lines of visual improvement was significantly higher in HBOT-treated patients with both CRAO (55.6% vs 25.7%, $P = 0.003$) and BRAO (56.2% vs 5.0%, $P < 0.001$).

In contrast, the proportion achieving a final VA of ≤ 0.3 logMAR did not differ significantly between treatment groups in either subgroup.

Multivariable analyses

Results of the multivariable regression analyses are presented in Tables 4 and 5.

Table 4. Multivariable linear regression models for final VA (logMAR)

Predictor	β (95% CI)	P value
CRAO subgroup (n = 122)		
Baseline VA (logMAR)	0.86 (0.57 to 1.14)	<0.001
HBOT treatment	-0.45 (-0.83 to -0.07)	0.020
Age (years)	0.02 (0.00 to 0.03)	0.010
Prior CVA	-0.32 (-0.86 to 0.23)	0.254
Hypertension	0.43 (0.09 to 0.76)	0.014
Male sex	-0.14 (-0.45 to 0.17)	0.378
Atrial fibrillation	-0.29 (-0.94 to 0.37)	0.384
BRAO subgroup (n = 56)		
Baseline VA (logMAR)	0.59 (0.43 to 0.75)	<0.001
HBOT treatment	-0.33 (-0.64 to -0.02)	0.035

Abbreviations: BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; CVA, cerebrovascular accident; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity.

Three CRAO patients were excluded from the respective models due to missing covariate data

Negative β coefficients indicate better final VA because lower logMAR values represent better vision.

Table 5. Multivariable linear regression models for visual improvement (Δ VA)

Predictor	β (95% CI)	P value
CRAO subgroup (n = 122)		
Baseline VA (logMAR)	-0.10 (-0.38 to 0.18)	0.475
HBOT treatment	-0.51 (-0.87 to -0.16)	0.005
Age (years)	0.02 (0.00 to 0.03)	0.012
Hypertension	0.43 (0.09 to 0.76)	0.014
Prior CVA	-0.34 (-0.88 to 0.20)	0.217
BRAO subgroup (n = 55)		
Baseline VA (logMAR)	-0.40 (-0.56 to -0.24)	<0.001
HBOT treatment	-0.33 (-0.64 to -0.01)	0.042
Age (years)	0.01 (-0.00 to 0.01)	0.201
Hyperlipidemia	0.11 (-0.19 to 0.40)	0.460
Ischemic heart disease	0.06 (-0.27 to 0.39)	0.717

Abbreviations: BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; CVA, cerebrovascular accident; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity; Δ VA, change in visual acuity.

Three CRAO and one BRAO patients were excluded from the respective models due to missing covariate data

Negative β coefficients indicate greater visual improvement because lower logMAR values represent better vision and more negative Δ VA values represent greater improvement.

For final VA, baseline VA was independently associated with worse final VA in both CRAO and BRAO (both $P < 0.001$). In the CRAO subgroup, increasing age ($\beta = 0.02$, $P = 0.010$) and hypertension ($\beta = 0.43$, $P = 0.014$) were independently associated with worse final VA. After adjustment for measured baseline covariates, HBOT remained independently associated with better final VA in both the CRAO ($\beta = -0.45$, $P = 0.020$) and BRAO ($\beta = -0.33$, $P = 0.035$) subgroups. The adjusted models explained 31% and 49% of the variance in final VA in the CRAO and BRAO subgroups, respectively.

For visual improvement (Δ VA), HBOT remained independently associated with greater visual improvement after adjustment for measured baseline covariates in both the CRAO ($\beta = -0.51$, $P = 0.005$) and BRAO ($\beta = -0.33$, $P = 0.042$) subgroups. In the CRAO subgroup, increasing age and hypertension were independently associated with less visual improvement. In the BRAO subgroup, poorer baseline VA was independently associated with greater visual improvement. The adjusted models explained 23% and 48% of the variance in Δ VA in the CRAO and BRAO subgroups, respectively.

Exploratory analyses

Results of the prespecified exploratory analyses among HBOT-treated patients with CRAO are presented in Table 6.

Table 6. Exploratory multivariable analyses of factors associated with visual outcomes among HBOT-treated patients with CRAO

Predictor	β (95% CI)	P value
Final VA (logMAR) (n = 88)		
Baseline VA (logMAR)	0.74 (0.20 to 1.27)	0.008
Time to presentation (0–4.5 h vs 4.5–8 h)	0.32 (–0.19 to 0.82)	0.215
Age (years)	0.02 (0.00 to 0.03)	0.017
Hypertension	0.44 (–0.02 to 0.89)	0.060
Atrial fibrillation	–0.30 (–1.04 to 0.44)	0.427
Visual improvement (ΔVA) (n = 88)		
Baseline VA (logMAR)	–0.12 (–0.61 to 0.38)	0.645
Time to presentation (0–4.5 h vs 4.5–8 h)	0.31 (–0.19 to 0.81)	0.221
Age (years)	0.02 (0.00 to 0.03)	0.033
Hypertension	0.46 (0.01 to 0.91)	0.045
Prior CVA	–0.53 (–1.21 to 0.15)	0.127

Abbreviations: CRAO, central retinal artery occlusion; CVA, cerebrovascular accident; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity; Δ VA, change in visual acuity.

Negative β coefficients indicate better final VA in the first model and greater visual improvement in the Δ VA model because lower logMAR values represent better vision and more negative Δ VA values represent greater improvement.

Poorer baseline VA remained independently associated with worse final visual acuity, while increasing age was associated with both poorer final vision and less visual improvement. Hypertension was associated with reduced visual improvement and showed a borderline association with worse final VA.

Patients presenting within 4.5 hours of symptom onset demonstrated numerically better visual outcomes than those presenting between 4.5 and 8 hours; however, these differences did not remain

statistically significant after multivariable adjustment (Figs. 3 and 4).

Safety

These analyses included all 134 patients who were treated with HBO, irrespective of eligibility for the comparative efficacy analyses.

No documented episodes of central nervous system oxygen toxicity, seizures, or treatment discontinuation due to HBOT-related adverse events were identified. Minor adverse events were infrequent and included ear pain (10%), sinus discomfort (4.5%), mild confinement anxiety (3%), and otoscopic abnormalities consistent with Teed grade 1–2 barotrauma (4.5%). Pressurization time exceeded 10 minutes in 17% of patients, most commonly because of difficulty equalizing middle ear pressure. No severe treatment-related adverse events were documented.

Discussion

In this retrospective cohort of patients with non-arteritic retinal artery occlusion (RAO) managed according to a predefined institutional treatment protocol, HBOT-treated patients demonstrated significantly greater visual improvement than untreated patients. Although final visual acuity (VA) did not differ significantly between treatment groups in unadjusted analyses, HBOT remained associated with better adjusted final VA and greater improvement in visual acuity in both central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO). These associations were observed despite substantially poorer baseline visual acuity among HBOT-treated patients, indicating that the observed findings persisted despite differences in presenting disease severity. The absence of significant differences in unadjusted final VA, despite greater visual improvement in the HBOT group, deserves consideration. Patients receiving HBOT presented with substantially poorer baseline vision than untreated patients, leaving greater potential for measurable recovery while simultaneously reducing the likelihood of achieving good absolute visual acuity at follow-up. Baseline VA is a major determinant of final visual outcome in retinal artery occlusion,[3, 8, 22, 23] and change in VA interpreted alongside baseline-adjusted analyses may better capture recovery than final VA alone in cohorts with baseline imbalance.[27] The magnitude of this baseline imbalance was substantial, a mean difference of approximately 0.5 logMAR in CRAO and 0.8 logMAR in BRAO, meaning that regression to the mean alone would be expected to inflate apparent HBOT-group improvement independent of any treatment effect. Adjusting for baseline VA as a covariate only partially addresses this bias. The persistence of the HBOT association across adjusted final VA and Δ VA models suggests a consistent association, although residual confounding and regression to the mean cannot be excluded. Our findings are broadly consistent with previous retrospective studies reporting improved visual outcomes following HBOT in CRAO.[19–24, 28, 29] However, existing studies differ substantially in treatment eligibility, timing of HBOT initiation, treatment protocols, outcome measures, and duration of follow-up. Consequently, systematic reviews and meta-analyses have concluded that the overall certainty of evidence remains limited despite encouraging observational data.[25, 26] Rather than resolving this uncertainty, the

present study adds evidence from a large, protocol-based cohort managed over more than two decades. By restricting the comparative analyses to patients treated according to a predefined institutional HBOT eligibility protocol, the study improves comparability between treatment groups and reduces heterogeneity in treatment allocation relative to many previous retrospective series. The recently published THEIA and TenCRAOS randomized trials further illustrate the challenges of establishing effective treatment for acute CRAO.[13, 14] Neither intravenous alteplase nor Tenecteplase significantly improved visual outcomes compared with standard therapy despite treatment within 4.5 hours of symptom onset. Direct comparison with the present study is limited by substantial differences in study design, intervention, and patient selection. Nevertheless, the observed association between HBOT and visual improvement in our cohort supports further prospective evaluation of HBOT.

The biological rationale for HBOT remains plausible. Increasing dissolved oxygen in plasma may permit oxygen diffusion from the choroidal circulation to the ischemic inner retina, thereby maintaining retinal metabolism until spontaneous or therapeutic reperfusion occurs.[15–17] Although this mechanism has been demonstrated experimentally, the extent to which it translates into sustained functional recovery in humans remains uncertain and is likely influenced by treatment timing, retinal viability, and the completeness of arterial occlusion. HBOT was well tolerated in our cohort, with no documented severe treatment-related adverse events, supporting its feasibility when administered in experienced centers.

Several baseline characteristics were independently associated with visual outcomes. Poorer presenting VA consistently predicted worse final visual acuity, reflecting the severity of the initial ischemic insult. Older age and hypertension were associated with poorer outcomes in CRAO, possibly reflecting reduced retinal resilience and greater underlying vascular disease. Within the BRAO subgroup, poorer baseline VA was associated with greater improvement, likely reflecting a larger dynamic range for recovery rather than superior final visual outcomes.

The exploratory analyses among HBOT-treated patients with CRAO also provide insight into factors potentially influencing treatment response. Earlier presentation was associated with numerically greater visual improvement, although these associations did not remain statistically significant after multivariable adjustment. These findings should be interpreted cautiously because the subgroup analysis was limited by sample size. Nevertheless, the observed direction of effect is consistent with experimental evidence demonstrating progressive retinal injury following arterial occlusion[30] and with previous observational studies suggesting greater benefit from earlier HBOT initiation.[22, 29] Recent meta-analytic evidence similarly supports earlier treatment as a potential determinant of improved visual outcomes, although substantial between-study heterogeneity remains.[26]

This study has several strengths. The cohort was assembled from consecutive patients treated at a tertiary referral center over a 24-year period and included both CRAO and BRAO. Importantly, comparative analyses were restricted to patients managed consistently with a predefined institutional treatment protocol, thereby reducing heterogeneity in treatment allocation. In addition, adjustment for measured baseline differences enabled evaluation of treatment associations while accounting for

important prognostic variables, including presenting visual acuity. Several limitations should also be considered. The retrospective observational design precludes causal inference and remains susceptible to residual confounding despite multivariable adjustment, as treatment allocation was not randomized and unmeasured clinical factors may have influenced both treatment decisions and outcomes. Baseline visual acuity differed substantially between treatment groups, and although adjustment for baseline VA was incorporated into all multivariable models, regression to the mean and residual confounding cannot be fully excluded. The study also spans more than two decades, during which referral patterns, diagnostic imaging, and clinical management evolved.

Documentation of conservative interventions administered before HBOT was incomplete, particularly among HBOT-treated BRAO patients (missing in 37.5%), reflecting inconsistent recording over the 24-year study period rather than a structured data-collection exclusion. This limits the reliability of acute-management comparisons in this subgroup and leaves the possibility of residual confounding from undocumented interventions. Finally, conversion of profound visual impairment categories to fixed logMAR values may have reduced measurement precision, and follow-up intervals were not standardized; therefore, visual outcomes reflect routine clinical practice rather than predefined assessment time points.

In conclusion, HBOT was independently associated with greater visual recovery in patients with both CRAO and BRAO within this protocol-based retrospective cohort. Because treatment allocation was not randomized, these findings should be interpreted as demonstrating an association rather than a causal treatment effect. Nevertheless, the consistency of the observed associations across multiple visual outcome measures, together with the biological rationale for HBOT and the limited effectiveness of currently available therapies, supports continued prospective evaluation of HBOT in prospective multicenter observational studies and randomized clinical trials.

Declarations

Competing interests

The author(s) declare no competing interests

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Author Contribution

E.Z. contributed to conceptualization, investigation, data curation, formal analysis, and writing of the original draft, and participated in manuscript review and editing. L.M. contributed to data curation.

W.A.A. contributed to methodology, formal analysis, and validation. G.A. contributed to data curation. I.G. contributed to investigation and data curation. I.B. contributed to conceptualization, methodology, and manuscript review and editing. N.D.S. contributed to conceptualization, methodology, investigation, data curation, visualization, writing of the original draft, manuscript review and editing, supervision, and project administration. All authors reviewed the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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Data Availability

The data that support the findings of this study are available from Rambam Health Care Campus, but restrictions apply to the availability of these data because they contain potentially identifiable patient information and are subject to institutional and ethical restrictions; therefore, they are not publicly available. The data are, however, available from the corresponding author upon reasonable request and with permission of Rambam Health Care Campus.

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Figures

Figure 1. Flow diagram of patient selection and final analytic cohort.

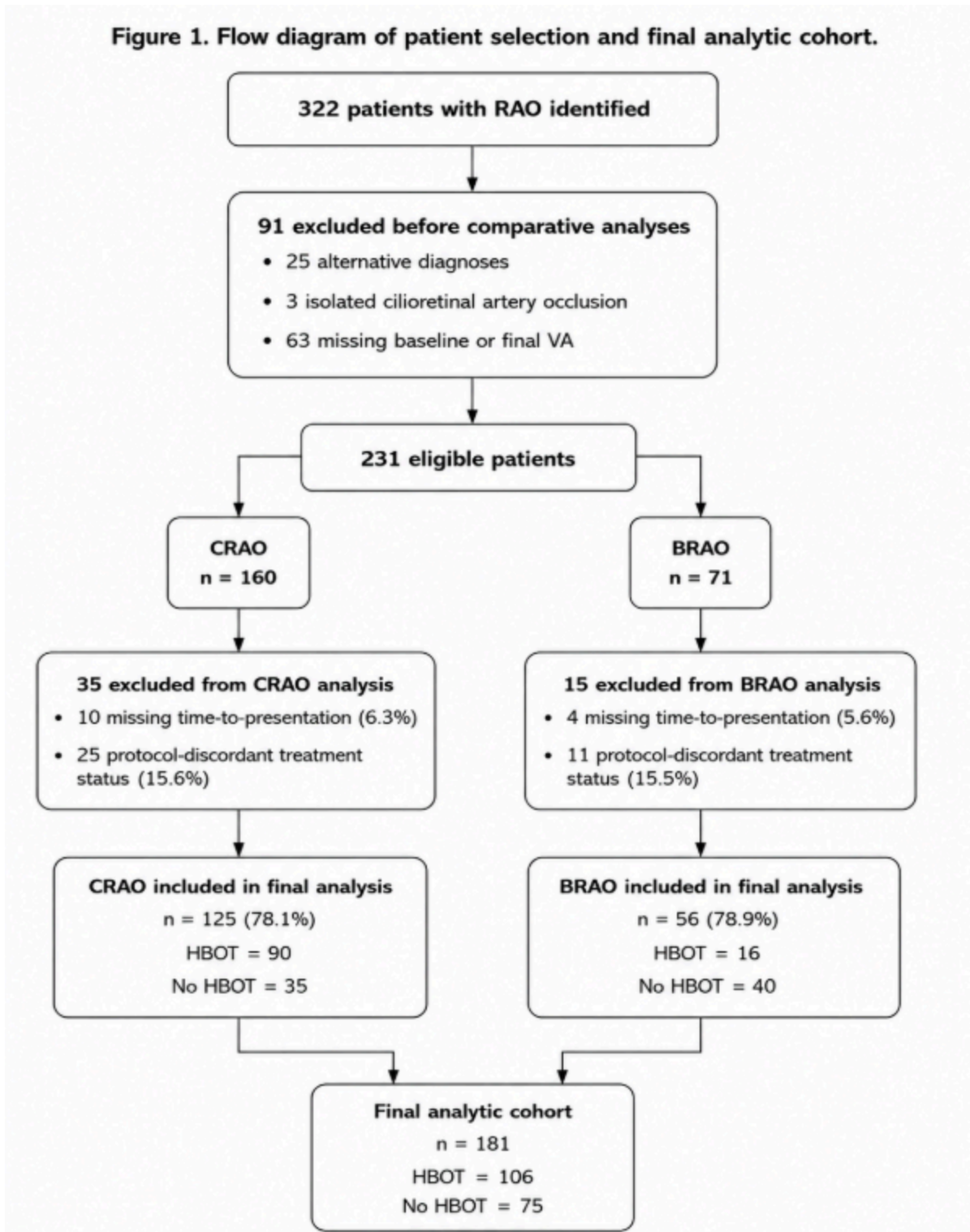


Figure 1

Flow diagram of patient selection and final analytic cohort. Patients were identified retrospectively from consecutive cases of retinal artery occlusion diagnosed between January 2000 and December 2023. Comparative analyses were restricted to patients managed consistently with the predefined institutional HBOT eligibility protocol. Protocol-inconsistent treatment comprised 12 CRAO and 4 BRAO patients who received HBOT despite presenting >8 hours after symptom onset, and 13 CRAO and 7 BRAO patients who did not receive HBOT despite presenting within the institutional 8-hour treatment window.

Abbreviations: VA, visual acuity; BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; HBOT, hyperbaric oxygen therapy; RAO, retinal artery occlusion.

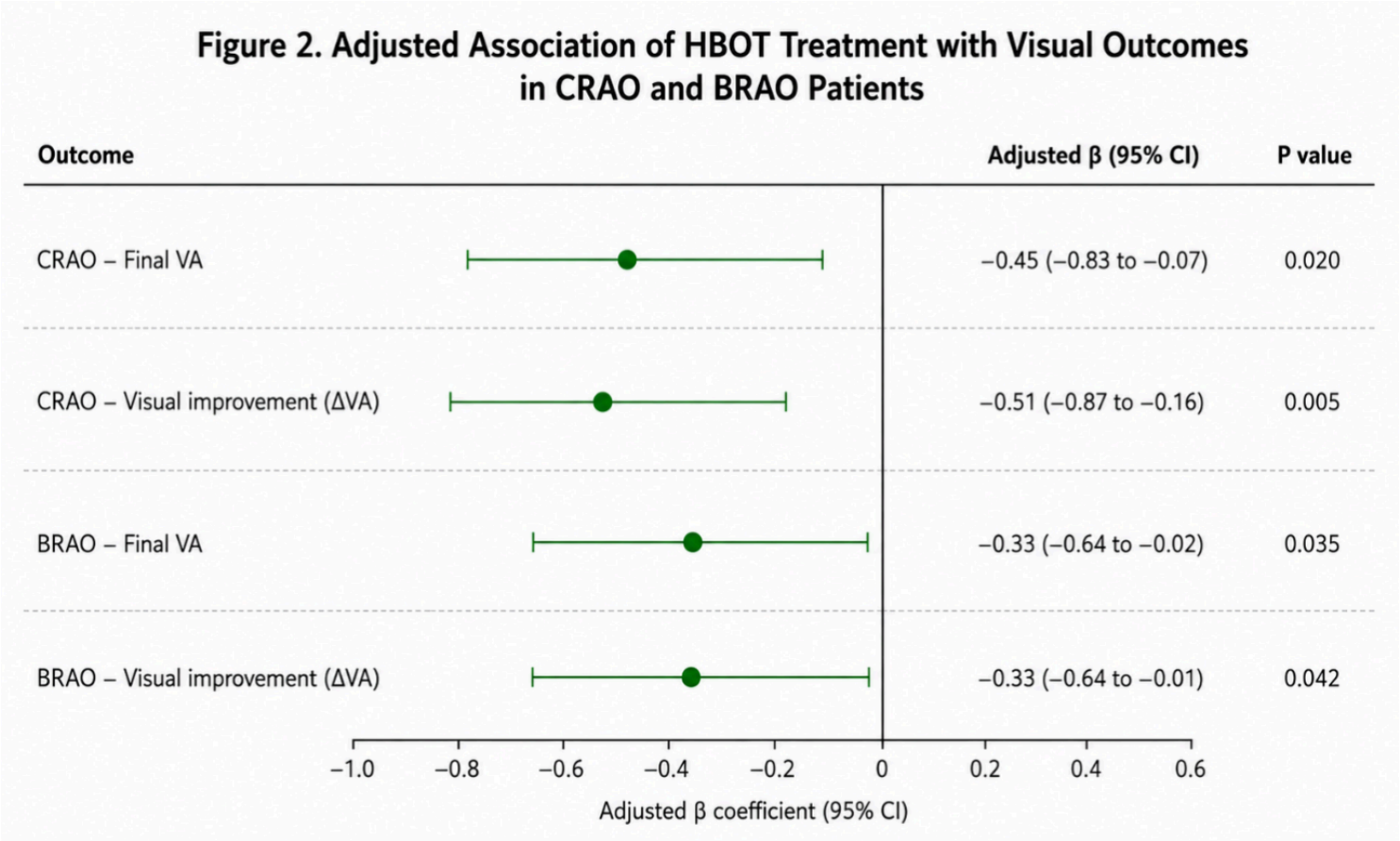


Figure 2

Forest plot showing the adjusted β coefficients and 95% confidence intervals from multivariable linear regression models evaluating the association between HBOT and visual outcomes in patients with CRAO and BRAO. Separate models are shown for final visual acuity (VA) and visual improvement (Δ VA). Negative β coefficients indicate better visual outcomes associated with HBOT because lower logMAR values represent better visual acuity.

Abbreviations: BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; CI, confidence interval; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity; Δ VA, change in visual acuity.

Figure 3. Final visual acuity according to presentation time.

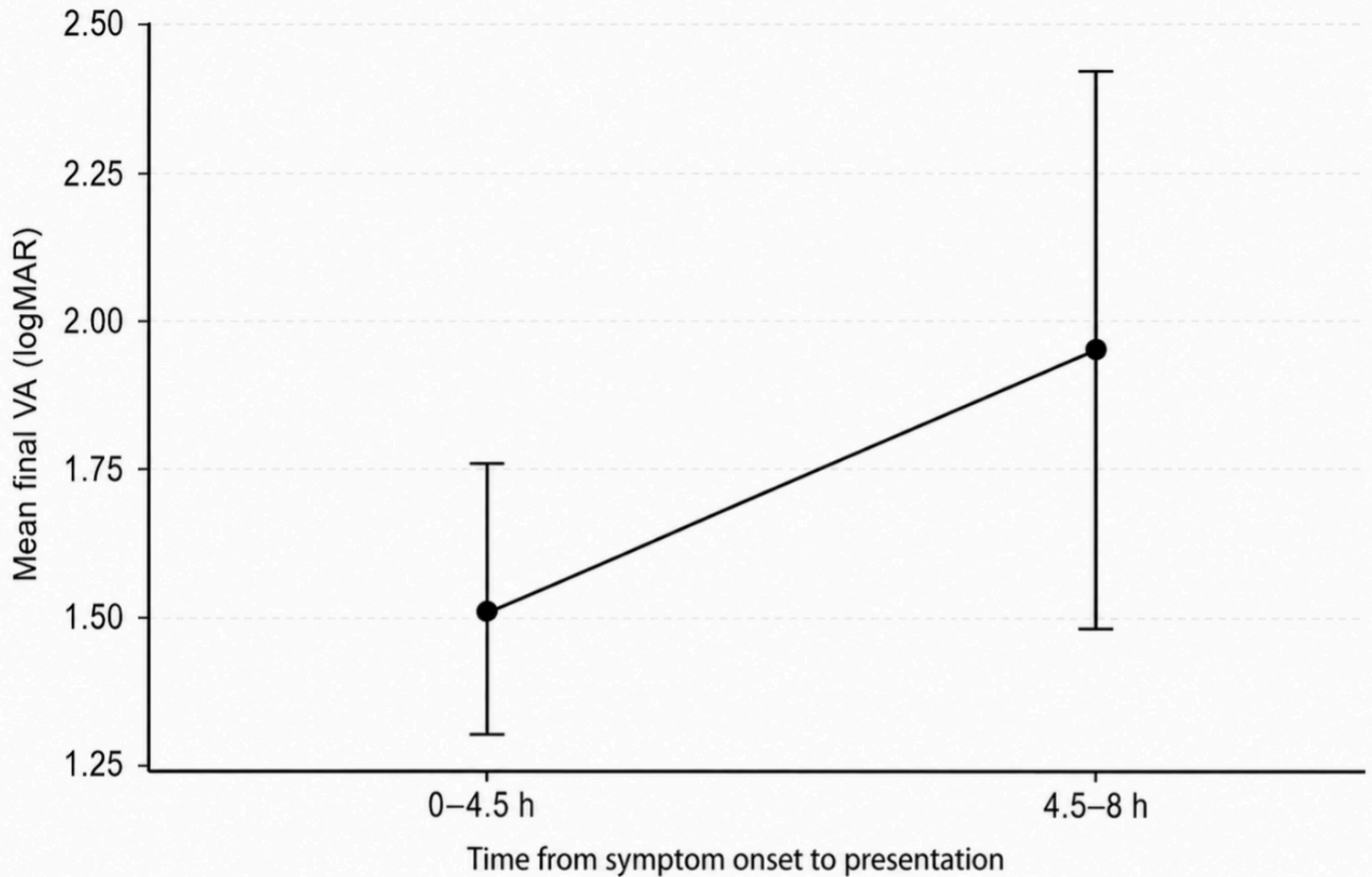


Figure 3

Final visual acuity according to time from symptom onset to emergency department presentation. Mean final visual acuity (VA) is shown for patients presenting within 0-4.5 hours and 4.5-8 hours after symptom onset. Error bars represent standard deviations.

Abbreviations: CRAO, central retinal artery occlusion; ER, emergency room; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; Δ VA, change in visual acuity.

Figure 4. Visual Improvement according to presentation time.

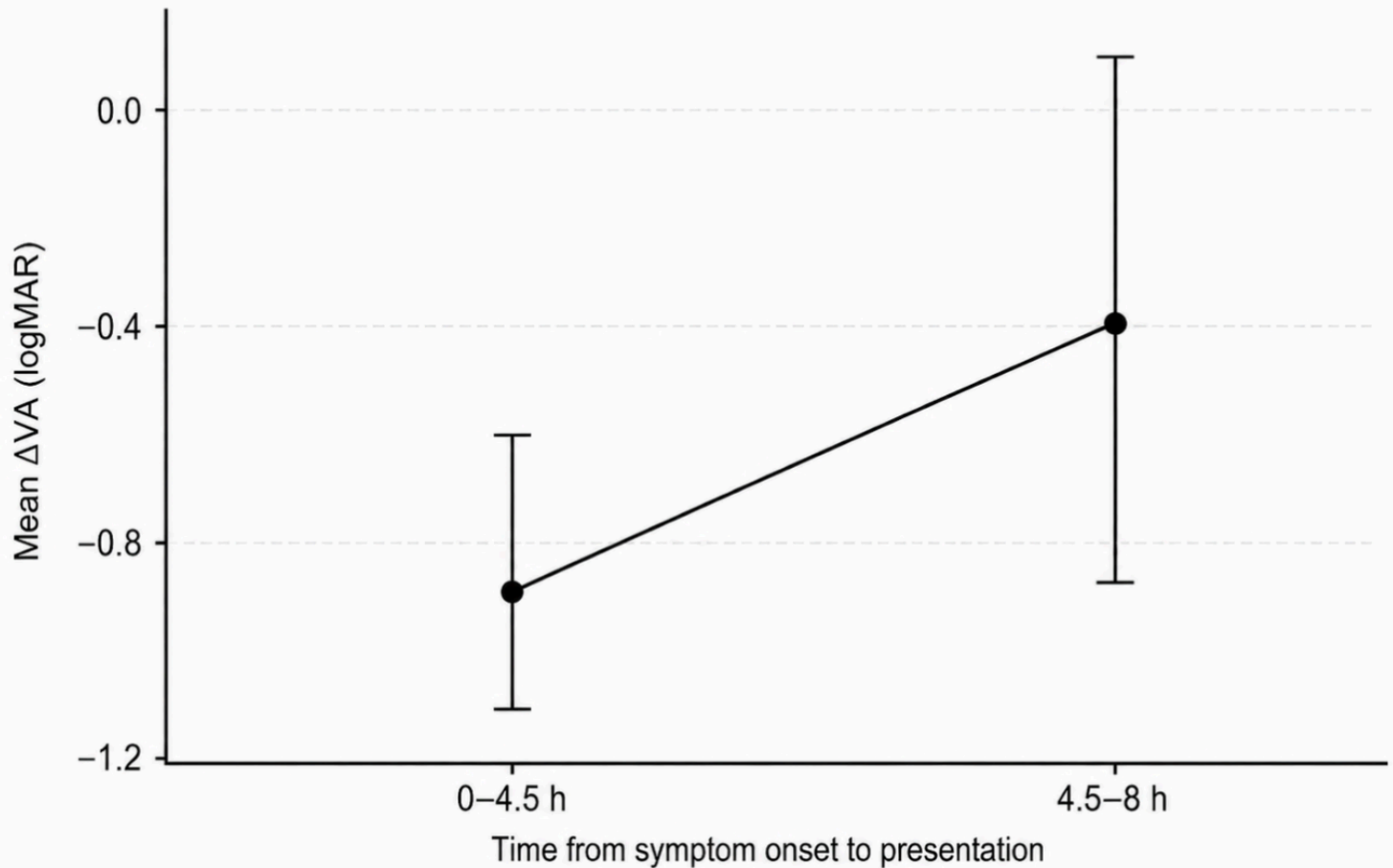


Figure 4

Visual improvement according to time from symptom onset to emergency department presentation.

Mean change in visual acuity (ΔVA) is shown for patients presenting within 0–4.5 hours and 4.5–8 hours after symptom onset. Error bars represent standard deviations. More negative ΔVA values indicate greater visual improvement.

Abbreviations: ΔVA , change in visual acuity; logMAR, logarithm of the minimum angle of resolution.