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Effectiveness of Repetitive Hyperbaric Oxygen Therapy for Chronic Limb-Threatening Ischemia

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Background: Lower extremity artery disease is strongly associated with morbidity and is typically addressed through revascularization interventions. We assessed the clinical outcomes of patients with chronic limb-threatening ischemia (CLTI) without revascularization who did and did not undergo repetitive hyperbaric oxygen therapy (HBOT).

Methods: Between April 2002 and March 2017, the records of 58 patients with CLTI (Rutherford classification 4 in 19% and 5 in 81%) were evaluated retrospectively. HBOT was performed at 2.8 atm of oxygen (HBOT group). The control group included those who could not continue HBOT and historical controls. Patients in poor general health or with an indication for revascularization therapy were excluded. We examined major adverse events (MAEs) and limb salvage rates. Independent predictors and risk stratification were analyzed using a multivariate regression analysis.

Results: The mean age was 71±13 years. Of all patients, 67% had diabetes and 43% were undergoing hemodialysis. The mean follow-up period was 4.3±0.8 years. The overall survival rate was 84.5% and 81.0% at 1 and 3 years, respectively. The Cox regression analysis indicated that high body mass index (odds ratio [OR]: 0.86; 95% confidence interval [CI]: 0.76-0.97; p=0.01), well-nourished (OR: 1.21; 95% CI: 1.01-1.45), and HBOT (OR: 0.05; 95% CI: 0.01-0.26; p<0.001) independently predicted absence of MAEs. For major limb amputation, the ankle-brachial index (OR: 0.2; 95% CI: 0.05-0.86; p=0.03) and HBOT (OR: 0.04; 95% CI: 0.004-0.32; p=0.003) were independent predictors.

Conclusions: Repetitive, stand-alone HBOT was associated with MAE-free survival and limb salvage in patients with CLTI. (J Nippon Med Sch 2024; 91: 66–73)

Key words: hyperbaric oxygen therapy, chronic limb-threatening ischemia, lower extremity artery disease

Introduction

Lower extremity artery disease (LEAD) is strongly associated with concomitant coronary and cerebrovascular diseases[1–3]. Subsequent life expectancy worsens in cases of lower-limb amputation[4–6]. A multidisciplinary approach, including possible revascularization by a vascular specialist, is mandatory for limb salvage[1]. However, few alternative treatment options are available when revascularization is not indicated or when an intractable condition, such as unhealed ischemic ulcers or re-occlusion of treated vessels, is identified[1]. Considering the need for oxygen delivery in limb ischemia[2], hyperbaric oxygen therapy (HBOT) may be beneficial for patients with chronic limb-threatening ischemia (CLTI) who do not respond to revascularization[7]. In this study, we tested the hypothesis that HBOT would improve CLTI outcomes and investigated the therapeutic effects of repetitive HBOT for patients with CLTI for whom revascularization was not indicated.

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Materials and Methods

Study Design

In this single-center cohort study patients were recruited retrospectively from the LEAD registry, which included consecutive patients with an ankle-brachial index (ABI) of <0.9 who had been referred to Nippon Medical School Hospital between 2002 and 2017. The patients were considered for inclusion if they had CLTI, confirmed by angiography or contrast-enhanced computed tomography, which suggested lower-limb arterial occlusion, with rest pain or a refractory leg ulcer that did not improve with standard treatment[1]. The exclusion criteria were (i) eligibility for revascularization, with malignant neoplasms within 5 years of treatment, and (ii) cognitive impairment or critical illness in patients in poor general condition who could not provide informed consent, could not be transferred to the HBOT room, or had a contraindication for HBOT, such as ear infection, sinusitis, or severe emphysema.

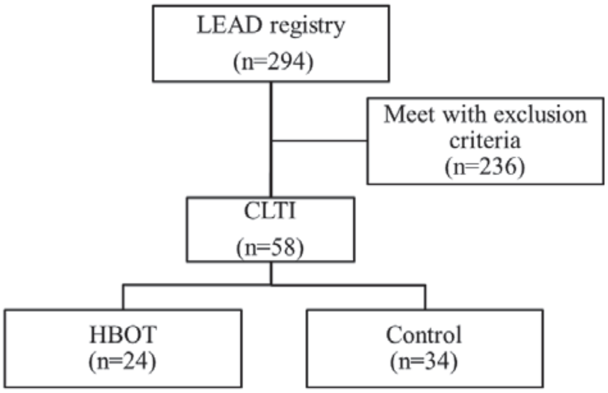

Fig. 1 Flowchart of patient enrollment
The flowchart presents data for patients with CLTI from the LEAD registry. Using the exclusion criteria, we excluded 236 patients; 58 patients were enrolled in the study.
CLTI, chronic limb-threatening ischemia; HBOT, hyperbaric oxygen therapy; and LEAD, lower extremity artery disease

The indications for revascularization therapy at our center were reviewed based on the opinions of cardiologists and cardiovascular surgeons. Because of the limited therapeutic options for ischemic limbs, all patients were scheduled to undergo HBOT. The patients for whom HBOT was possible were designated as the HBOT(eligible) group. Those who were could not begin or continue

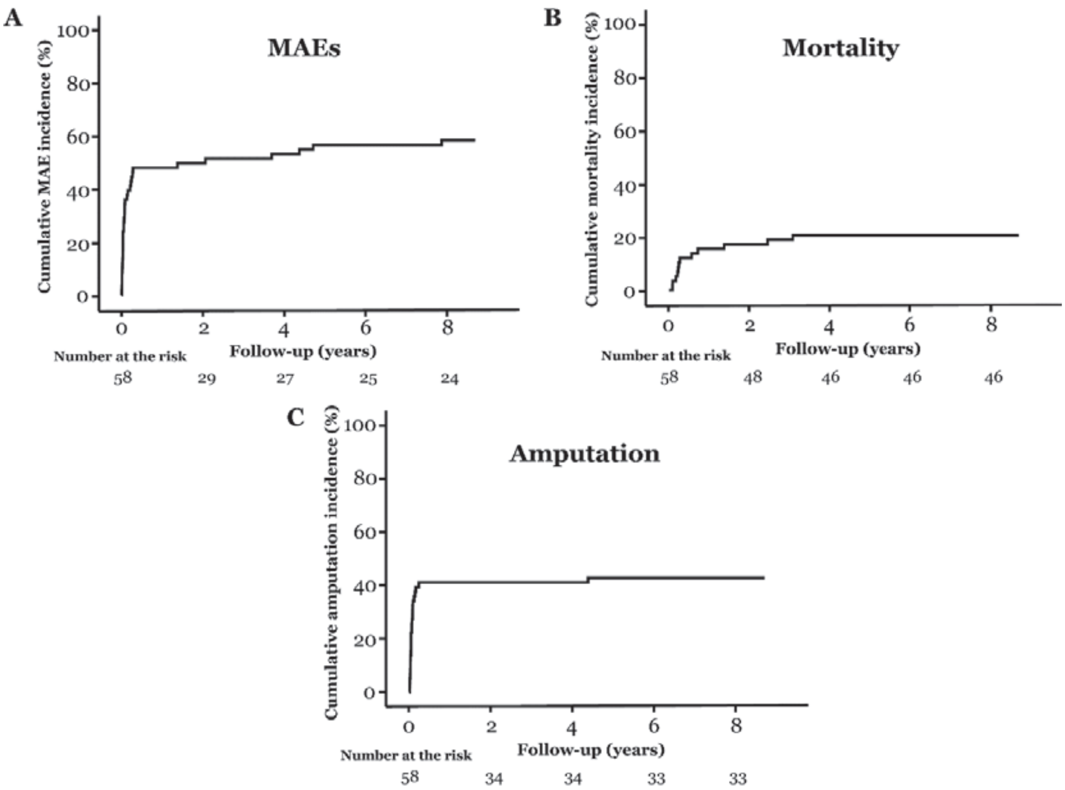

Fig. 2 Kaplan-Meier curves for cumulative incidence of MAEs (A), mortality (B), amputation (C)
The curves present the primary outcomes, i.e., a composite of major adverse events and limb amputation (Panel A); the components of mortality (Panel B); and above-the-knee and below-the-knee amputation (Panel C). Data are represented during an 8-year follow-up.
MAEs, major adverse events

Table 1 Patient characteristics

	All patients (n=58)	Control (n=34)	HBOT (n=24)	*p*-value
Age – years	70.9±12.9	72.8±13.2	68.3±12.1	0.19
Sex – male/female no. (male %)	40/18 (69)	24/10 (71)	16/8 (67)	0.19
Foot ulcer – no. (%)	47 (81)	29 (85)	18 (75)	0.19
Rest pain – no. (%)	11 (19)	5 (15)	6 (25)	0.19
Type 2 diabetes mellitus – no. (%)	39 (67)	22 (65)	17 (71)	0.24
Receiving hemodialysis – no. (%)	23 (40)	20 (59)	3 (13)	0.001
Ischemic ulcer – no. (%)	47 (81)	29 (85)	18 (75)	0.50
Receiving aspirin – no. (%)	21 (36)	16 (47)	5 (21)	0.13
Receiving statin – no. (%)	11 (19)	4 (12)	7 (29)	0.13
White blood cell count – µL	8,983±4,861	9,647±5,808	8,042±2,930	0.19
C-reactive protein – mg/dL	5.27±7.65	6.62±7.13	3.36±8.11	0.90
CONUT score	4.52±3.08	5.35±2.82	3.33±3.10	0.02
ABI	0.60±0.3	0.57±0.3	0.64±0.3	0.19

Values are presented as the mean±SD.
ABI, ankle brachial pressure index; CONUT score, Controlling Nutritional Status score; and HBOT, hyperbaric oxygen therapy

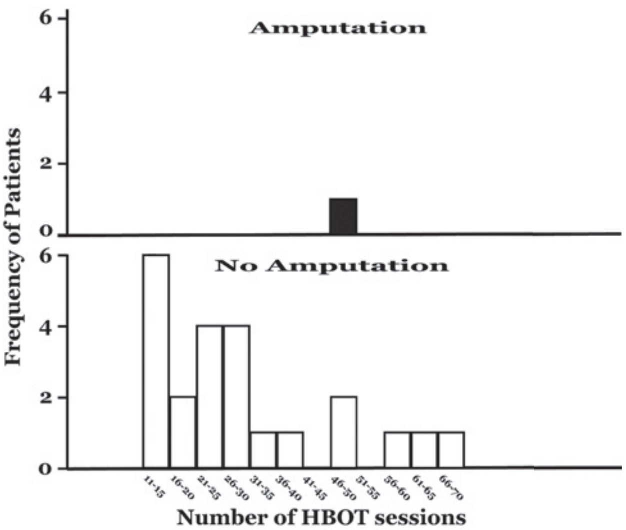

Fig. 3 Histogram of HBOT sessions in the HBOT group
Limb amputation events are shown in the upper panel (black bar), and numbers of patients with no amputations are shown in the lower panel (white bars).
HBOT, hyperbaric oxygen therapy

HBOT (fewer than five sessions) because of technical difficulties, such as difficulty in equalizing ear pressure, or mental conditions, such as claustrophobia, were designated as the control group. In addition, historical controls (without HBOT) were added to the control group (**Fig. 1**). The primary endpoint was incidence of major adverse events (MAEs), such as death, below-knee or above-knee amputation, or any event requiring hospital admission. Incidence of limb amputation, i.e., below-knee or above-knee amputation, was set as the secondary endpoint. Follow-up was continued in the outpatient clinic.

Wound Management

For patients with unresolved pain at rest, the HBOT protocol was continued under management with oral nonsteroidal anti-inflammatory drugs, neuropathic pain medications, opioids, and patient-controlled analgesia with an intravenous opioid pump. If the ulcer site was concurrently infected, a bacterial culture (with a swab or tissue specimen) was performed, and appropriate antibiotics were administered with iodine or silver ion-containing ointments. Prostaglandin E1-containing ointments were used to treat uninfected wounds. The gangrenous area was resected to the maximum extent possible, and frequent washing with saline solution was performed after debridement when there was a risk of abscess. Wound dressings, negative-pressure wound therapy, and gauze protection were used to promote wound healing, as determined by the wound bed condition. Debridement or osteotomy was performed for patients who developed gangrene or osteomyelitis confirmed by radiography and ^{67}Gallium single-photon emission computed tomography (SPECT)/CT[8,9], according to the physician's decision.

HBOT

We used the BTH P-2200S HBOT system (Barotech Hanyuuda Inc.) and performed HBOT with 100% oxygen mask inhalation at an absolute atmospheric pressure of 2.8 for 60 min per session, repeated for 6 days per week. HBOT was continued until pain at rest or the foot ulcer improved, as determined by the attending physician. After completing HBOT, patients who returned to a family practice for further management were followed up with

Table 2 Univariate and multivariate analyses for MAEs

	Univariate analysis		p-value	Multivariate analysis		p-value
	Odds ratio	95% CI		Odds ratio	95% CI	
Age	1.01	0.98–1.04	0.41			
Male sex	0.76	0.36–1.63	0.49			
Body mass index	0.91	0.83–0.99	0.03	0.86	0.76–0.97	0.01
White blood cell count	1.00	1.00–1.00	0.005	1.00	1.00–1.00	0.18
Type 2 diabetes mellitus	0.90	0.41–1.97	0.80			
Receiving hemodialysis	3.21	1.54–6.68	0.002	2.00	0.71–5.63	0.19
History of smoking	1.41	0.65–3.07	0.38			
Ischemic ulcer	2.27	0.79–6.52	0.13			
CONUT score	1.22	1.08–1.37	0.002	1.21	1.01–1.45	0.04
ABI	3.34	0.10–1.10	0.07	0.32	0.09–1.17	0.84
HBOT performed	0.06	0.02–0.20	<0.001	0.05	0.01–0.26	<0.001

CONUT score, Controlling Nutritional Status score; ABI, ankle brachial pressure index; HBOT, hyperbaric oxygen therapy; CI, confidence interval; and MAEs, major adverse events

Table 3 Univariate and multivariate analyses for major limb amputation

	Univariate analysis		p-value	Multivariate analysis		p-value
	Odds ratio	95% CI		Odds ratio	95% CI	
Age	1.01	0.98–1.04	0.51			
Male sex	0.84	0.54–1.29	0.42			
Body mass index	0.94	0.85–1.03	0.16			
White blood cell count	1.00	1.00–1.00	0.005	1.00	1.00–1.00	0.06
Type 2 diabetes mellitus	0.67	0.51–2.88	0.67			
Receiving hemodialysis	2.97	1.48–5.96	0.002	1.10	0.45–2.67	0.83
History of smoking	1.24	0.52–2.95	0.63			
Ischemic ulcer	2.15	0.64–7.18	0.21			
CONUT score	1.22	1.07–1.40	0.003	1.03	0.87–1.21	0.75
ABI	0.19	0.05–0.68	0.01	0.20	0.05–0.86	0.03
HBOT performed	0.03	0.004–0.24	<0.001	0.04	0.004–0.32	0.003

CONUT score, Controlling Nutritional Status score; ABI, ankle brachial pressure index; HBOT, hyperbaric oxygen therapy; and CI, confidence interval

a telephone outcome survey. We used intention-to-treat analysis to determine treatment effectiveness.

Statistical Analyses

We analyzed the frequency of HBOT until symptom improvement or wound healing. The incidence of MAEs was verified to evaluate the efficacy of HBOT implementation in patients with CLTI. Cut-off values were obtained using maximum sensitivity and specificity based on the Youden Index. Outcomes were compared between the two groups with Cox hazard regression analysis yielding unadjusted hazard ratios with 95% confidence intervals (CIs). To determine the risk difference in the incidence of MAEs and major limb amputation between patients with and without HBOT, univariate and multivariate regression analyses of cumulative incidence were performed. For multi-regression analysis, Cox regression analysis was adjusted for known risk factors, such as age, sex, smoking history, foot ulcers, diabetes, receipt of hemodialysis, white blood cell count, nutritional status, and ABI. Nutritional status was assessed by the Controlling/Nutritional Status (CONUT) score[10], which is calculated from the serum albumin level, total cholesterol level, and total lymphocyte count with weighting. A p-value of <0.1 in univariate analysis was included in multivariate analysis. For the endpoint analysis, a two-sided p-value of <0.05 was considered statistically significant. All other analyses are reported with 95% CI. Statistical analysis was performed using SPSS software (version 28, IBM Corporation, Armonk, NY, USA).

Ethical Considerations

This study was performed at the Nippon Medical School Hospital. The protocol was covered by the Japanese national insurance system. The study was approved by the ethics committee of Nippon Medical School and

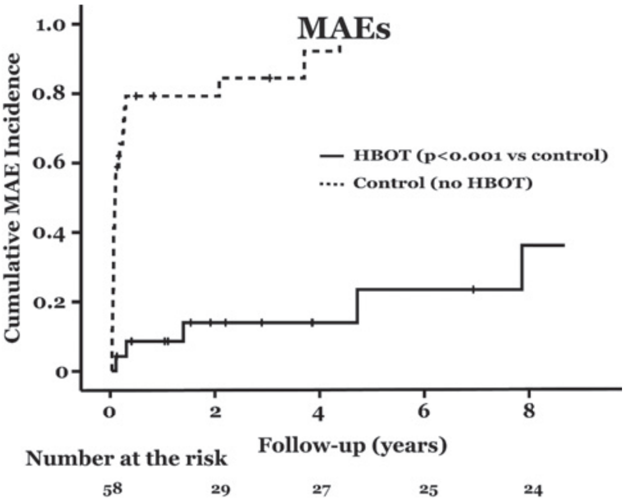

Fig. 4 Kaplan-Meier curves for the primary outcome
The curves present the primary outcome—a composite of major adverse events and limb amputation—among patients in the HBOT and control groups. There was a significant difference between the groups.
HBOT, hyperbaric oxygen therapy; MAEs, Major adverse events

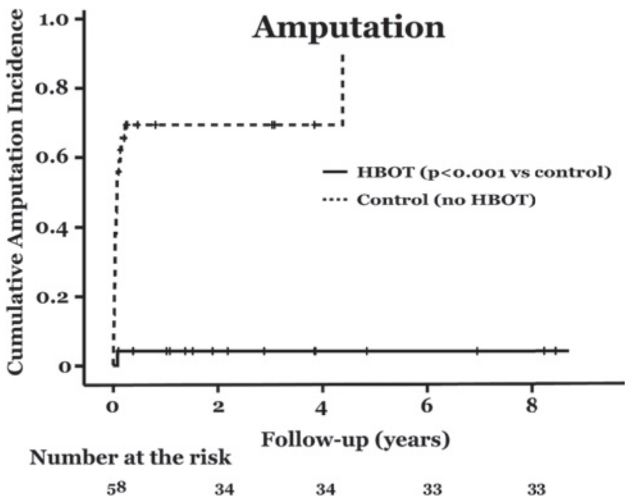

Fig. 5 Kaplan-Meier curves for the secondary outcome
The curves present the secondary outcome—limb amputation events—among patients in the HBOT and control groups. There was a significant difference between the groups.
HBOT, hyperbaric oxygen therapy

performed in accordance with the ethical standards of the Declaration of Helsinki. The protocol was registered with the University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR), which is accepted by the International Committee of Medical Journal Editors (no. UMIN000004112).

Results

Participants

Between April 2002 and March 2017, 294 patients were enrolled in the LEAD registry. In accordance with the inclusion and exclusion criteria, 58 patients were enrolled in this study (**Fig. 1**). All ulcers were followed until healing unless an adverse event occurred. After a mean follow-up of 4.3±0.8 years, 34 (58.6%) patients experienced an MAE: 12 (20.7%) died and 25 (43.1%) underwent a major amputation (**Fig. 2**). The control group had more hemodialysis patients and higher CONUT scores, but there were no between-group differences in other baseline characteristics (**Table 1**). The use of the protocol resulted in eight (13%) patients being switched to the control group because they could not continue HBOT (HBOT fewer than five sessions) due to technical difficulties. Overall survival was 84.5% and 81.0% at 1 and 3 years, respectively. Partial osteotomy was performed in 32 (55%) patients. The cause of death in the non-HBOT group was sepsis (in five patients), cardiovascular disease (in three patients), neoplasm (in one patient), and cholecystitis (in one patient). In the HBOT group, one patient had cardiovascular disease and one had sepsis.

Histogram

Figure 3 is a histogram of the HBOT frequency in the HBOT group. The average HBOT frequency was 11.3±16.3 sessions. The frequency decreased gradually in patients who had been cured. Only one patient had a below-the-knee amputation, and ulcers had healed in the remaining patients. The attending physician decided on the necessity for continuing HBOT by examining the depth and area of the ischemic ulcer. HBOT frequency was not associated with the limb amputation event rate (p=0.31, 95% CI: 0.95-1.17) or MAEs (p=0.26, 95% CI: 0.98-1.09). The incomplete dropout rate of HBOT until wound healing was 0% in the HBOT group.

Endpoint

Regarding primary endpoints, body mass index, CONUT score, and HBOT were independent risk factors (p=0.01, 0.04, and <0.001, respectively; **Table 2**). Cox regression analysis of major limb amputation indicated that ABI (p=0.03) and HBOT (p=0.003) were independent risk factors, and white blood cell count tended to be significant (**Table 3**). Cox regression analysis showed a significant difference between the control and HBOT groups in MAEs (p<0.001 vs. control by log-rank test, **Fig. 4**) and amputation (p<0.001 vs. control by log-rank test, **Fig. 5**). **Figure 6** is a forest plot based on the multi-regression analysis. Subgroup analyses implicated HBOT, in analyses of MAEs and amputations (p<0.001 for MAEs; p=

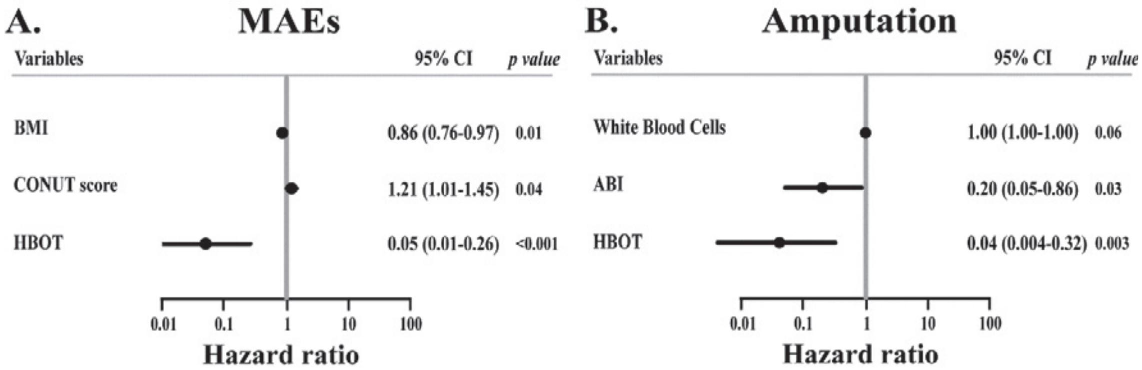

Fig. 6 Forest plot of subgroup analysis of MAEs (A) and amputation risk (B) of HBOT
The widths of confidence intervals are adjusted for the multi-regression analysis.
MAEs, major adverse events; HBOT, hyperbaric oxygen therapy; BMI, body mass index; CONUT, controlling nutritional status; and CI, confidence interval

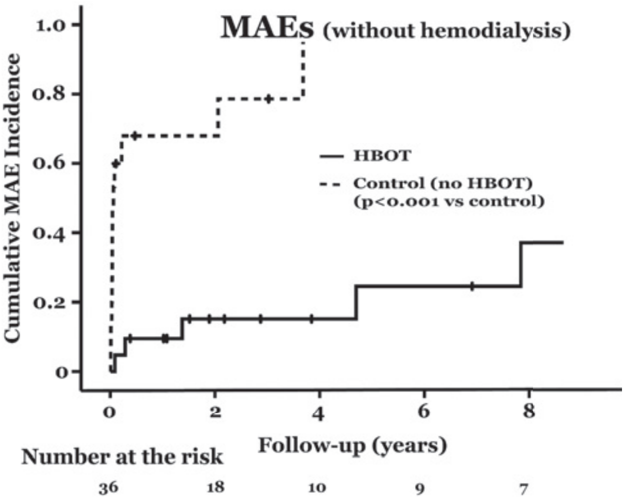

Fig. 7 Kaplan-Meier curves for the primary outcome in non-hemodialysis patients
The curves present the primary outcome—a composite of major adverse events and limb amputation—among patients in the HBOT and control groups without hemodialysis. There was a significant difference between groups.
HBOT, hyperbaric oxygen therapy; MAEs, major adverse events

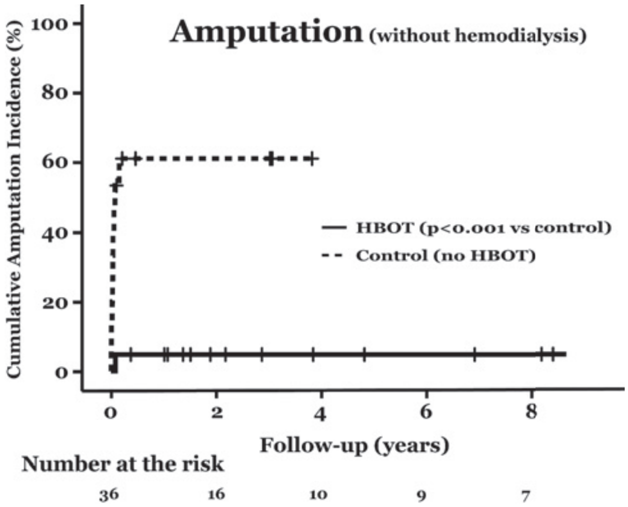

Fig. 8 Kaplan-Meier curves for the secondary outcome in non-hemodialysis patients
The curves present the secondary outcome—limb amputation events—among patients in the HBOT and control groups without hemodialysis. There is a significant difference between the groups.
HBOT, hyperbaric oxygen therapy

0.003 for amputations), and the ABI, in the amputation analysis (p=0.03 for amputation), as independent predictors. There were no obvious differences in other variables. Furthermore, because of significant differences in the presence of hemodialysis treatment at baseline, the results of analysis excluding patients undergoing hemodialysis are included as supplementary analyses (**Figures 7, 8**).

Discussion

Several studies have demonstrated the therapeutic benefits of HBOT for LEAD. Specifically, HBOT prevents amputation by increasing transcutaneous oxygenation[11], improves wound healing after 1 year of treatment[12], and enhances long-term outcomes[12,13]. In patients with ischemic ulcers, HBOT can prevent bacterial growth by inducing reactive oxygen species[14]. Similarly, we observed therapeutic benefits of HBOT on CLTI during both the acute phase and long-term follow-up. However, studies have reported limited efficacy of HBOT in patients with

LEAD[15,16]. Notably, these studies may not accurately reflect clinical efficacy, as they included >20% dropouts and patients with mild ischemia and did not consider prolonged treatment cycles according to the severity of ischemia. Despite the initiation of a registry study in Japan[17], the number of effective treatments, dropout rates, and patient selection by indication have not been clarified.

In this study, the frequency-based HBOT applied in actual clinical practice differed from the approach specified in the CLTI guidelines[18], which state that HBOT should be performed in combination with revascularization procedures. However, the event rate did not increase when HBOT was used as a complementary procedure in patients who were not candidates for revascularization. Interestingly, there were no cases of treatment discontinuation, and patients were able to continue treatment until complete recovery or self-management.

This cohort study had limitations. It was not randomized because of the presence of non-optional patients, which may have introduced selection bias for HBOT. In addition, the study sample was small.

In summary, repetitive noninvasive HBOT was an independent predictor in patients with CLTI, and repetitive HBOT may contribute to MAE-free survival and limb salvage.

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Conflict of Interest: The authors declare no conflicts of interest.

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