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TITLE PAGE

Indications, therapeutic modalities and clinical outcomes of hyperbaric oxygen therapy in Italy, the ITA-OTI Study:

A multicentre prospective observational study

Mariachiara Ippolito[1,2*], Luca Martani[3], Alberto Noto[4], Laura Maniscalco[5], Giulia Spurio[1], Marina Nasello[2], Salvatore Sardo[6], Vincenzo Francesco Tripodi[4], Savino Borraccino[7], Luigi Giancarlo Vicari Sottosanti[7], Carlotta Ferraro[8], Luca Cantadori[3], Andrea Neville Cracchiolo[9], Luigi Targa [10], Fiorenzo Fracasso [11], Andrea Giovaniello [12], Fiammetta Ronga[2], Claudio Spena[13], Elena Giovanna Bignami[8], Domenica Matranga[5], Antonino Giarratano[1,2], Andrea Cortegiani[1,2] and SIAARTI Study Group

[*]**Correspondence to**: Mariachiara Ippolito, MD, Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C), University of Palermo, 90127 Palermo, Italy, Department of Anaesthesia, Intensive Care and Emergency, Policlinico Paolo Giaccone, Via del Vespro 129, 90127 Palermo, Italy

e-mail: mariachiara.ippolito@unipa.it

[1] Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C), University of Palermo, 90127 Palermo, Italy

[2] Department of Anaesthesia, Intensive Care and Emergency, Policlinico Paolo Giaccone, Via del Vespro 129, 90127 Palermo, Italy

[3] Anesthesiology, Critical Care and Hyperbaric Medicine Unit, Vaio Hospital, AUSL Parma, Fidenza, Italy

[4] Division of Anesthesia and Intensive Care, Department of Human Pathology of the Adult and Evolutive Age "Gaetano Barresi", Policlinico "G. Martino," University of Messina, Messina, Italy

[5] Division of Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialities, University of Palermo, Palermo, Italy

[6] Department of Medical Sciences and Public Health, University of Cagliari, 09042, Monserrato, Italy

[7] Anesthesia and Intensive Care Complex Unit, Cannizzaro Emergency Hospital, Catania, Italy

[8] Anesthesiology, Critical Care and Pain Medicine Division, Department of Medicine and Surgery, University of Parma, Viale Gramsci 14, 43126, Parma, Italy

[9] Unit of 118 Emergency Medical Services and Hyperbaric Medicine, ARNAS Civico Di Cristina Benfratelli Hospital, Palermo, Sicily, Italy

[10] Domus Medica Private Clinic, San Marino, Republic of San Marino

[11] Taranto Military Hospital - Hyperbaric Medicine Service, Taranto, Italy

[12] Hyperbaric Oxygen Therapy Unit, Habilita - Casa di Cura I Cedri, Fara Novarese, Italy

[13] Emergency Department, SSD Emergency plans management – ATS Liguria - ASL2, San Paolo Hospital, Savona, Italy

ABSTRACT

Background: Real-world data describing contemporary hyperbaric oxygen therapy (HBOT) practice in Italy are limited. This study aimed to describe current clinical indications and therapeutic modalities of HBOT at national level.

Methods: We conducted a multicenter, prospective, observational national study, promoted by Italian Society of Anesthesia Analgesia, Resuscitation and Intensive Care (SIAARTI). We included consecutive patients who underwent HBOT in 10 study centers within a period of 12 weeks, for any treatment indication. The primary outcome of the study was the proportion of treatments by clinical indication and urgency of treatment.

Results: Overall, 327 patients were included across 10 centres, of which 73.7% (n=241) received elective and 26.3% (n=86) urgent treatments. The most frequent indication was sudden hearing loss (35.8%), followed by carbon monoxide poisoning (19.9%) and soft tissue infection (12.2%). Treatments were delivered at a median of 2.5 ATA, with two oxygen cycles for session and a median of 16 sessions for patients. No serious adverse events occurred.

Conclusions: In Italy, HBOT is applied in accordance with national and international guidelines. The most frequent indications to treatment were sudden hearing loss, carbon monoxide poisoning, and soft tissue infections. Treatments had similar characteristics across the centres, with heterogeneity mainly regarding the number of sessions per patients.

Clinical trial number: Not applicable.

Keywords: Hyperbaric oxygen therapy; Italy; observational; prospective

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) is a therapy exploiting the physiological effects of delivering cycles of 100% O_2 breathing at an increased atmospheric pressure to enhance oxygen availability at the tissue level. Within the hyperbaric chamber, patients breathe oxygen at supraphysiological partial pressures, resulting in a marked increase in the amount of oxygen dissolved in plasma and facilitating oxygen diffusion to tissues independently of hemoglobin-mediated transport. This mechanism allows effective oxygen delivery to areas characterized by hypoxia, impaired perfusion, or altered oxygen-carrying capacity, overcoming some of the limitations of conventional normobaric oxygen therapy (1). Beyond enhanced oxygen delivery, the therapeutic effects of HBOT include modulation of inflammatory pathways, improvement of host immune response, stimulation of angiogenesis, and bacteriostatic and bactericidal activity, particularly in hypoxic or poorly perfused tissues (2).

Specific structural and safety requirements should be met to grant patients' safety during the procedures and clinical contraindications must be ruled out (3). HBOT has established clinical effectiveness in acute conditions, such as decompression sickness, dysbarism disorders and carbon monoxide (CO) poisoning, as well as in selected chronic ischemic, infectious, and inflammatory conditions (4).

However, the implementation of HBOT in clinical practice remains heterogeneous across the centres. In Italy, the most recent national guidelines for hyperbaric medicine date back to 2015 (4), while European consensus recommendations were published in 2017 (5).

Geographical variability may further contribute to determine heterogeneity in case mix, treatment indications, and clinical workload among hyperbaric facilities. For instance, hyperbaric centers located in coastal regions are more frequently involved in the treatment of decompression illness related to recreational and occupational diving activities. Conversely, centers operating in mountainous or inland areas more commonly manage

cases of carbon monoxide poisoning, often associated with domestic heating systems such as wood-burning or gas stoves. In addition to clinical and geographical variability, organizational differences may play a significant role in shaping HBOT practice, in terms of availability for on-call emergency treatments. To date, comprehensive real-world data describing the current practice of hyperbaric medicine in Italy are limited.

The aim of the present study was to describe current clinical practice of hyperbaric oxygen therapy in Italy and provide an overview across different clinical indications and organizational models, with the purpose of generating real-world data that may support future research and harmonization of HBOT practice. Indeed, the study was not designed to assess causal effectiveness, but rather to describe real-world indications, treatment modalities and short-term outcomes of HBOT across multiple centres.

METHODS

We conducted a prospective, observational, multicentre national study, promoted by Italian Society of Anesthesia Analgesia, Resuscitation and Intensive Care (SIAARTI). The study was conducted in full respect of the Helsinki Declaration and was approved by the Human Ethical Committees of the centres (first approval Palermo I, 08/04/2024). The overall period of study spanned from April 2024 to October 2025. Before the beginning of the study period, a national call was opened, and all the active hyperbaric centres were invited to join the study through the network provided by SIAARTI. Over two years, 10 centres were able to join and obtained approval by their Ethical Committees, as per national regulations. We considered eligible all the patients consecutively referred to the hyperbaric oxygen therapy services at the 10 participating centers. Each centre enrolled patients for 12 consecutive weeks starting at a convenience start date after formal approval by their Ethical Committees. Therefore, the enrollment windows were staggered across centres over the overall 18-month study period (April 2024–October 2025).

Patients were included after the collection of a written informed consent to participate. Patients who refused to provide consent or who had already received hyperbaric treatments for the same disease prior to the study period were excluded. For each patient, data collection took place at baseline (i.e. first access to the hyperbaric chamber), at the end of each session of therapy and at 30-day follow-up after the last treatment cycle.

The primary outcome of the study was the proportion of treatments by clinical indication and urgency of treatment. As part of data-cleaning procedures, entries reporting multiple concurrent indications were recorded by merging them into a single category based on the clinically dominant indication, to ensure consistency and analytical comparability.

We also sought characteristics of the treatments used and their relative frequency, proportion of patients with complete clinical resolution at 30 days follow-up, proportion of patients with partial clinical resolution of the disease (defined as "any benefit" compared to the previous condition) at 30 days follow-up after the last treatment cycle, and treatment related adverse events as secondary exploratory outcomes. The categorization of cases in elective or urgent was performed by the local investigator, i.e. the hyperbaric physician.

The study took place with a prospective collection of data from medical records through the electronic database RedCap, provided by Italian Society of Anesthesia Analgesia, Resuscitation and Intensive Care (SIAARTI). Data were collected in pseudonymized form. Data on the characteristics of the centres, regarding the technical characteristics of the hyperbaric chamber and the characteristics of the dedicated team were also collected.

The patient's status at 30-day after the last treatment cycle was assessed by one of the study investigators and clinical resolution was established based on non-standardized clinical judgment of the treating specialist (e.g. ear nose throat specialist for sudden hearing loss) and/or by the investigator, expert in hyperbaric medicine during a follow-up visit or a follow-up phone call, with no pre-specified indication-specific criteria to define resolution.

The study results were reported adhering to the STROBE statement (6) and the checklist is available at Supplementary Material. Clinical trial number: not applicable.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and range, as appropriate according to their distribution. Categorical variables were reported as frequencies and percentages. Group comparisons were performed to assess differences between subgroups. Continuous variables were compared using the Student's *t*-test or the Wilcoxon rank-sum test, depending on the normality assumption. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical analyses were performed using R software (version 4.5.1, R Foundation for Statistical Computing, Vienna, Austria) by LM and MI, with supervision by DM and input by AC. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 389 patients were treated during the period of study in the participating centres.

A flow-diagram showing details on inclusion-exclusion process is available in Supplementary Material. As 62 patients were excluded according to exclusion criteria, the final cohort consisted of 327 included patients, of which 73.7% (n=241) received elective and 26.3% (n=86) urgent treatments. Table S1, Supplementary Material, shows urgency of treatments per participant centres.

Most adhering centres were public institutions (75%), active on a 7/7-day basis (62.5%). Despite recent indications issued by the national scientific society, many centres declared no availability of mandatory monitoring systems (e.g. for vital parameters) or devices for their routine treatments: mechanical ventilator was available in 80% of the centres, SpO2 and EKG monitoring was available in 60% of the centres and temperature was only available in 20% of centres. On average, the centres declared having a median of 6 [5-8] physicians, 5 [2-6] nurses and 3 [2-5] hyperbaric technicians in their dedicated team. Physicians were

certified anaesthetists in eight of the ten centres, while two centres had a proportion of anaesthetists ranging from 20% to 50% of the medical staff. The median patients' capacity of the centres was 8 patients [8 - 8] per session. Most of the centres joined the study during 2025 (8/10), with the promoting centre only conducting the study between April and July 2024 and another centre conducting the study between November 2024 and February 2025. Of note, only two centres selected study period during winter season.

Characteristics of the included patients

Median age of the included patients was 54 years [42-65] and 58.7% of the patients were males. Characteristics of the included patients at admission are presented in **Table 1**. The most represented comorbidity was diabetes (5.8%), and most patients had no comorbidities (63.3%). The most frequent indication to receive hyperbaric oxygen therapy was sudden hearing loss (35.8%), followed by carbon monoxide poisoning (19.9%), mixed or anaerobic soft tissue infections (12.2%) and chronic ulcers (8.9%). A total of twelve patients were of pediatric age and **Table S2, Supplementary Material**, shows their baseline characteristics. **Figure 1** shows the proportion of treatments by urgency and indications.

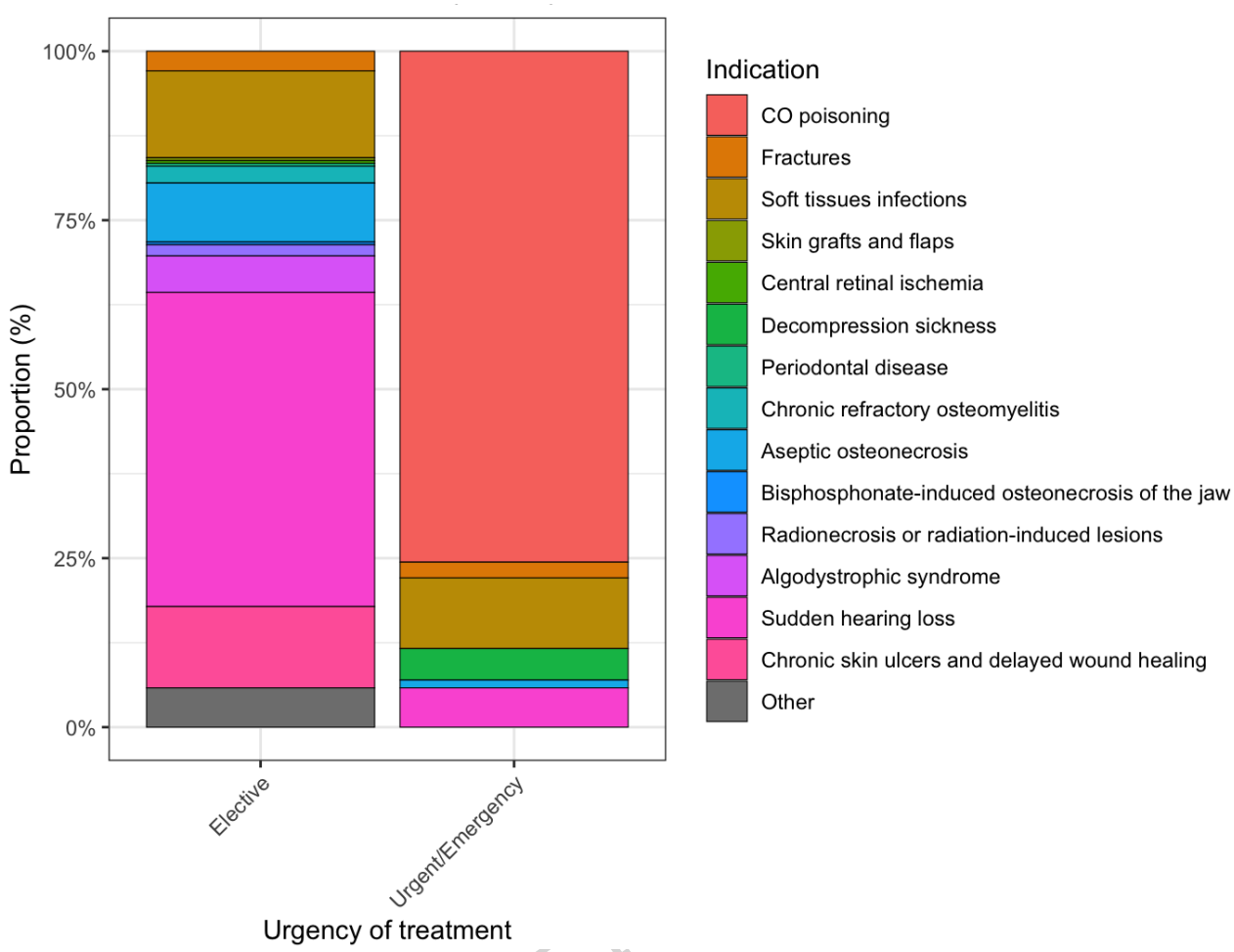

Figure 1. Proportion of treatments by urgency and indications

Hyperbaric oxygen treatment was suggested by surgeons in most of the cases (45.6%), followed by emergency department physicians (19.3%), with a very low prevalence of indications coming from general practitioners (3.1%). Blood count and biochemistry lab results were missing in more than half patients, witnessing the non-mandatory nature of lab results to confirm indication to the treatment. Blood pressure and heart rate were on average within normal values at admission. Chest X-ray was performed in 76.5% of the cases as screening of contraindications, with significant difference between urgent/emergency treatments and elective ones (52.3% vs. 85.1%; P<0.001). Despite such a wide application of X-ray, 99.4% of the patients showed no signs of barotrauma. Audiometry was performed in 54.4% of the cases prior to start the treatment, more frequently in elective cases (70.1%) compared to urgent/emergency ones (10.5%, P<0.001). Overall, respiratory support had

different proportions across urgent and elective cases (P<0.001). No patients were under invasive or non-invasive mechanical ventilation, and most of the patients (82.9%) were breathing at room air at baseline assessment. Oxygen therapy was frequently adopted in case of patients with urgent indications (61.6%).

	Overall (N=327)	Elective (N=241)	Urgent (N=86)	P-value
Age				
Mean (SD)	52.5 (17.4)	55.4 (14.4)	44.5 (22.0)	**<0.001**
Median [Q1, Q3]	54.00 [42.00, 65.00]	57.00 [47.00, 66.00]	46.00 [27.00, 57.75]	
Sex				
F	135 (41.3%)	93 (38.6%)	42 (48.8%)	0.126
M	192 (58.7%)	148 (61.4%)	44 (51.2%)	
Weight (kg)				
Mean (SD)	73.5 (16.2)	75.8 (14.6)	67.0 (18.7)	**<0.001**
Median [Q1, Q3]	74.00 [65.00, 84.00]	75.00 [65.00, 85.00]	70.00 [61.00, 78.00]	
Comorbidities				
≥2	39 (11.9%)	32 (13.3%)	7 (8.1%)	0.902
Asthma	5 (1.5%)	3 (1.2%)	2 (2.3%)	
Diabetes	19 (5.8%)	14 (5.8%)	5 (5.8%)	
Congestive heart failure	1 (0.3%)	1 (0.4%)	0 (0%)	
Leukemia or lymphoma	1 (0.3%)	1 (0.4%)	0 (0%)	
Cerebrovascular disease	4 (1.2%)	3 (1.2%)	1 (1.2%)	
Connective tissue disease	1 (0.3%)	1 (0.4%)	0 (0%)	
Chronic lung disease	6 (1.8%)	5 (2.1%)	1 (1.2%)	
Renal disease	1 (0.3%)	1 (0.4%)	0 (0%)	
Peripheral vascular disease	17 (5.2%)	12 (5.0%)	5 (5.8%)	
Liver disease	1 (0.3%)	1 (0.4%)	0 (0%)	
Gastric disease	11 (3.4%)	10 (4.1%)	1 (1.2%)	
No comorbidities	207 (63.3%)	146 (60.6%)	61 (70.9%)	
Previous myocardial infarction	2 (0.6%)	1 (0.4%)	1 (1.2%)	
Any malignant tumor	12 (3.7%)	10 (4.1%)	2 (2.3%)	
Indications*				
Carbon monoxide poisoning or post interval syndrome	65 (19.9%)	0 (0%)	65 (75.6%)	**<0.001**
Exposed fractures with crush trauma or fractures at risk or crush injuries without fracture	9 (2.8%)	7 (2.9%)	2 (2.3%)	

Anaerobic and mixed infections (anaerobic myositis, necrotizing fasciitis, skin infections, necrotizing epidermal infections, diabetic gangrene)	40 (12.2%)	31 (12.9%)	9 (10.5%)	
Compromised or at-risk skin grafts and flaps	1 (0.3%)	1 (0.4%)	0 (0%)	
Central retinal ischemia	1 (0.3%)	1 (0.4%)	0 (0%)	
Decompression sickness	4 (1.2%)	0 (0%)	4 (4.7%)	
Periodontal disease	1 (0.3%)	1 (0.4%)	0 (0%)	
Refractory chronic osteomyelitis	6 (1.8%)	6 (2.5%)	0 (0%)	
Aseptic osteonecrosis	22 (6.7%)	21 (8.7%)	1 (1.2%)	
Bisphosphonate-induced mandibular osteonecrosis	1 (0.3%)	1 (0.4%)	0 (0%)	
Radionecrosis or radiation-induced injury	4 (1.2%)	4 (1.7%)	0 (0%)	
Algodystrophy syndrome	13 (4.0%)	13 (5.4%)	0 (0%)	
Sudden hearing loss	117 (35.8%)	112 (46.5%)	5 (5.8%)	
Chronic skin ulcers and delayed wound healing	29 (8.9%)	29 (12.0%)	0 (0%)	
Other	14 (4.3%)	14 (5.8%)	0 (0%)	
Height (cm)				
Mean (SD)	168 (12.3)	169 (8.04)	163 (19.3)	**0.024**
Median [Q1, Q3]	170.00 [163.00, 175.00]	170.00 [164.00, 175.00]	167.50 [160.00, 174.50]	
Who suggested hyperbaric treatment				
General practitioner	10 (3.1%)	10 (4.1%)	0 (0%)	**<0.001**
Hospital doctor (medical area)	37 (11.3%)	35 (14.5%)	2 (2.3%)	
Hospital doctor (surgeon)	149 (45.6%)	136 (56.4%)	13 (15.1%)	
Private doctor (medical area)	22 (6.7%)	21 (8.7%)	1 (1.2%)	
Private doctor (surgeon)	39 (11.9%)	38 (15.8%)	1 (1.2%)	
First aid	63 (19.3%)	1 (0.4%)	62 (72.1%)	
Out of hospital emergency service/118	7 (2.1%)	0 (0%)	7 (8.1%)	
Glasgow Coma Scale				
Mean (SD)	15.0 (0.118)	15.0 (0.0985)	15.0 (0.156)	0.335
Median [Q1, Q3]	15.00 [15.00, 15.00]	15.00 [15.00, 15.00]	15.00 [15.00, 15.00]	
Missing	41 (12.5%)	36 (14.9%)	5 (5.8%)	
Systolic blood pressure (mmHg)				
Mean (SD)	131 (17.8)	131 (16.8)	129 (20.0)	0.249

Median [Q1, Q3]	130.00 [120.00, 140.00]	130.00 [120.00, 140.00]	128.00 [115.00, 140.00]	
Missing	48 (14.7%)	45 (18.7%)	3 (3.5%)	
Diastolic blood pressure (mmHg)				
Mean (SD)	77.5 (10.8)	78.6 (11.0)	75.0 (9.85)	**0.019**
Median [Q1, Q3]	80.00 [70.00, 85.00]	80.00 [70.00, 85.00]	75.00 [70.00, 80.00]	
Missing	48 (14.7%)	45 (18.7%)	3 (3.5%)	
Mean arterial pressure (mmHg)				
Mean (SD)	94.8 (13.9)	96.0 (13.1)	92.1 (15.5)	0.072
Median [Q1, Q3]	95.00 [87.00, 103.00]	95.00 [88.00, 104.25]	93.00 [83.00, 103.00]	
Missing	48 (14.7%)	45 (18.7%)	3 (3.5%)	
Heart rate (beats per minute)				
Mean (SD)	78.5 (16.0)	74.1 (11.7)	89.1 (19.4)	**<0.001**
Median [Q1, Q3]	76.00 [67.00, 88.50]	74.00 [65.00, 81.00]	89.00 [74.00, 102.50]	
Missing	48 (14.7%)	45 (18.7%)	3 (3.5%)	
Respiratory support				
None	271 (82.9%)	238 (98.9%)	33 (38.4%)	**<0.001**
Oxygen therapy	56 (17.1%)	3 (1.2%)	53 (61.6%)	
Chest x ray				
No	77 (23.5%)	36 (14.9%)	41 (47.7%)	**<0.001**
Yes	250 (76.5%)	205 (85.1%)	45 (52.3%)	
Radiographic signs of barotrauma				
No	325 (99.4%)	239 (99.2%)	86 (100%)	1.000
Yes	2 (0.6%)**	2 (0.8%)**	0 (0%)	
Audiometry				
No	149 (45.6%)	72 (29.9%)	77 (89.5%)	**<0.001**
Yes	178 (54.4%)	169 (70.1%)	9 (10.5%)	

Table 1. Characteristics of the included patients at baseline, grouped by urgency of indication to treatment

Data are reported as median [Q1-Q3], mean (SD) and count (%) as appropriate. Continuous variables were compared using the Student's t-test or the Wilcoxon rank-sum test, depending on the normality assumption. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. * As part of data-cleaning procedures, entries reporting multiple concurrent indications were recorded by merging them into a single category based on the clinically dominant indication, to ensure consistency and analytical comparability.

** Patients assessed with CT scan prior to HBOT treatment and inclusion in the study. Radiological signs due to sequelae of previous and already treated conditions.

Treatments and outcomes

Table 2 shows the characteristics of the treatments performed. Overall, the median number of treatments was 16 [6-24] per patient, with only two patients receiving a single treatment. The median number of pure oxygen cycles (100% O_2 breathing at pressure, interspersed with air breaks) was 2 [2-3], with a median length of 30 minutes [20-30], at a median depth of 2.5 [2.5-2.5] ATA.

[TABLE 2 SHOULD APPEAR HERE IN THE MANUSCRIPT]

	Overall (N=327)
Number of oxygen cycles during the first session	
Mean (SD)	2.38 (0.724)
Median [Q1, Q3]	2.00 [2.00, 3.00]
Missing	1 (0.3%)
Depth	
Mean (SD)	2.49 (0.162)
Median [Q1, Q3]	2.50 [2.50, 2.50]
Missing	7 (2.1%)
Duration of each oxygen cycle	
Mean (SD)	28.2 (8.89)
Median [Q1, Q3]	30.00 [20.00, 30.00]
Missing	7 (2.1%)
Total session duration	
Mean (SD)	87.0 (14.7)
Median [Q1, Q3]	90.00 [86.00, 90.00]
Missing	7 (2.1%)
Total number of treatments	
Mean (SD)	18.6 (16.6)
Median [Q1, Q3]	16.00 [6.00, 24.00]
Missing	1 (0.3%)
Frequency of treatments	
Daily (Mon-Sun)	62 (19 %)
Daily excluding weekends (Mon-Fri)	198 (60.5%)
Single treatments	67 (20.5%)
Did the sessions following the first take place at the same depth and with the same combination and number of oxygen stops and duration?	
No	81 (24.8%)
Yes	246 (75.2%)
Type of resolution *	
Complete	154 (47.1%)
No resolution	44 (13.5%)
Partial	112 (34.3%)

Need for surgery or other treatment *	
No	226 (69.1%)
Yes	84 (25.7%)
Type of treatment	
Elective	241 (73.7%)
Urgent	86 (26.3%)

Table 2. Characteristics of treatments
Data are reported as median [Q1-Q3], mean (SD) and count (%) as appropriate.
*17 lost to follow up

Most of the treatments were performed with an unchanged setting or U.S. table after the first treatment (76.5%). We recorded 23 cases of treatment interruptions during sessions: 19 were due to difficult compensation and four were related to other non–life-threatening adverse events. Respectively ten patients out of 19 and one patient out of four did not continue with subsequent treatments, thus interrupting definitively the treatment. The other patients resumed the treatments in the days after the event. None of the interruptions was caused by technical issues or serious adverse events (SAEs). In one case, difficult compensation resulted in ear barotrauma requiring medical care after session interruption.

Overall, 25.7% of the patients required other therapies, including surgery, as co-interventions during the period of hyperbaric oxygen treatments.

We also divided the cohort based on the outcome achieved at 30-day follow-up. Seventeen patients were lost to follow-up. Our exploratory analysis based on non-standardized clinical assessment at 30-day follow-up after the last treatment cycle showed complete clinical resolution in 47.1%, while a partial resolution was registered in 34.3%. No benefits were registered in 13.5% of patients. Heterogeneity across indications and outcome measures limit such pooled results.

Figure 2 shows the outcome at 30-day follow-up after the last treatment per each of the main indications.

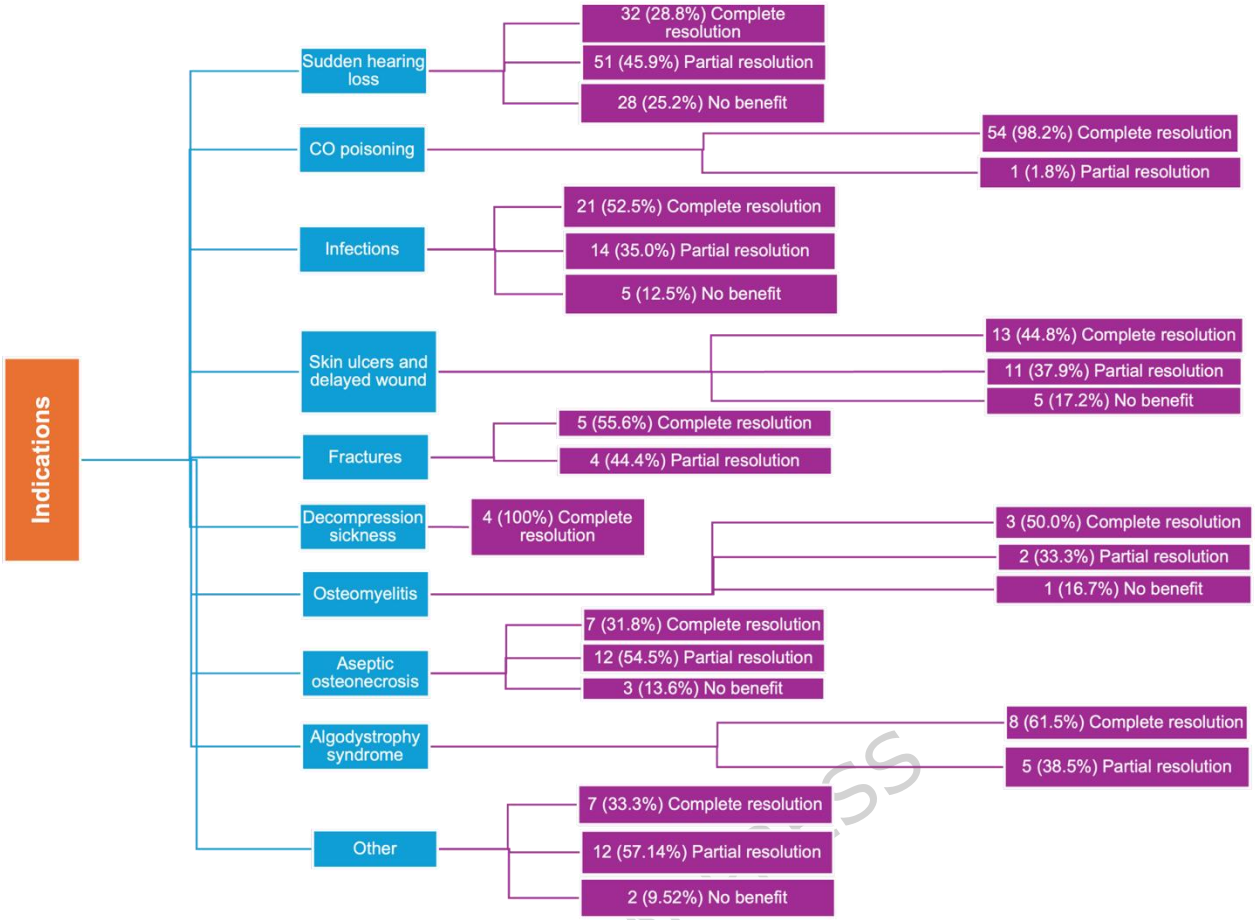

Figure 2. outcome at 30-day follow-up after the last treatment per each of the main indications

Regarding the most frequent indications, patients treated for sudden hearing loss had complete clinical resolution in 28.8% of the cases, partial benefit in 45.9% of the cases and no benefit in 25.2% of the cases. In patients treated for CO poisoning, complete clinical resolution was observed in 98.2% of the cases while one patient showed only partial benefit. Patients treated for soft tissue infections reached complete clinical resolution in 52.5%, partial benefit in 35% of the cases and no benefit in 12.5% of the cases.

Disease-specific baseline characteristics of the included patients are presented in the **Supplementary Material**, where multiple indications are reported as originally recorded, without recoding or merging.

DISCUSSION

We conducted the first large multicentre prospective observational study collecting data on hyperbaric oxygen therapy and clinical outcomes in Italy. Previous data were sparse and networking among Italian hyperbaric centres was challenged by resources availability, heterogeneity in local ethics committee approval pathways and heterogeneity of case-mix across the centres. Our experience witnesses the positive role of sharing homogeneous frameworks and scientific society support for research in the field of hyperbaric medicine.

Staffing and equipment of the participating centres were also surveyed, and such results provide insights at organizational level. For example, only two centres had a percentage of certified anesthetists among their hyperbaric physicians' teams below 50%, witnessing that residency program in anaesthesia and intensive care is the main pathway through which physicians get competences in this field in Italy, being also able to manage critical care, anaesthesia, airway control and emergencies. At present, no dedicated guidelines specify a minimum proportion or mandatory presence of anaesthetists for HBOT activities. Indeed, an in-depth analysis of medical specialties representation in Italian hyperbaric center was out of the scope of the study.

The most frequent indications to hyperbaric oxygen therapy were sudden hearing loss (35.8%), CO poisoning (19.9%) and soft tissue infections (12.2%), followed by other indication, less represented across the cohort. These are recognised, guideline-concordant indications for HBOT (4,5,7–11). When comparing our results with a wide international registry collecting data in US/UK/Australian centres from 2011 and published in 2022 (11), the proportion of sudden hearing loss among indications is quite higher, reflecting the Italian healthcare landscape (9).

A low proportion of other indications was registered (11), among which post-COVID-19 syndrome and fibromyalgia, that is currently receiving research interest but remain an off-label indication (12). We registered a wide heterogeneity in the proportion of indications

considered urgent or elective, witnessing that the distinction in urgent indication and elective indication is context-related in clinical practice. Indeed, sudden hearing loss and soft tissue infections were represented among both the urgent and elective indications. This heterogeneity may probably witness individual differences in time from disease onset or diagnosis to access to the treatment and differences in local clinical practice. From a methodological point of view, it may be due to the lack of pre-specified classification criteria in favor of real-world design.

Of note, we noticed heterogeneity also in pre-treatment screening assessments, such as X-ray. Emerging evidence suggests that routine pre-HBOT chest X-ray may not be universally indicated in the absence of clinical red flags (13), also given its low sensitivity and specificity. Our real-world data show that, in routine clinical practice, pre-HBOT chest X-ray is not indiscriminately applied as pre-treatment screening assessment. It can be argued that clinical examination and cost–benefit assessment by experienced physicians remain pivotal.

Treatments characteristics were overall homogenous across the centres in term of depth and number of oxygen cycles.

Hyperbaric oxygen therapy showed high safety profile, with no SAE and a very low prevalence of adverse events. Non-life-threatening adverse events occurred during HBOT sessions and are also well described in literature, usually due to ear discomfort and difficult compensation, claustrophobia, anxiety, hypoglycemia or headaches (14).

In our cohort, 25.7% of the patients received surgery or other treatments in the timespan from study inclusion and end of hyperbaric oxygen therapy cycles. It is reasonable to argue that most of the remaining had received other treatments before HBOT and that eventual complete clinical resolution was mainly reached with multidisciplinary care.

Indeed, HBOT should be interpreted as an adjunctive intervention rather than a standalone therapy, administered in addition to surgical management, antimicrobial therapy, advanced wound care, and disease-specific therapies.

Overall, the 30-day non-standardized clinical assessment found a high proportion of patients with resolution of the clinical condition indicating the treatment, but the exploratory nature of the analysis and the limits due to measurement bias of such outcome impede the drawn of any effectiveness conclusion. The observed real-world effectiveness should be interpreted with caution and put in the context of multidisciplinary care and biased assessment, but international literature including recent RCTs support HBOT as adjuvant treatment in many clinical indications.

Recently, a systematic review and meta-analysis reported that adjunctive HBOT was associated with reduced mortality and improved clinical outcomes, supporting its role in severe acute settings (15). Similarly, a large Scandinavian prospective multicenter cohort confirmed a survival benefit in patients receiving HBOT alongside standard care (7). In the context of chronic wound care, a recent randomized controlled trial demonstrated that HBOT significantly increased healing rates in patients with chronic venous ulcers compared with standard therapy alone (16). Sustained clinical improvement in patients with Crohn's disease–related perianal fistulas treated with HBOT has been found at one-year follow-up (17). Another pilot RCT found no statistically significant differences in radiation-induced dermatitis severity in patients with breast cancer treated with HBOT plus standard care, compared to standard care alone (18).

In this context of emerging evidence, it is remarkable that HBOT remains used in the context of approved indications and approved treatment protocols. Future research studies should be conducted, grounded on ethical and methodological basis, to respond to open research questions.

Our study has some limitations. First, the descriptive nature of our design, the lack of a control group and the low number of cases for some indications did not allow inferential analyses and limited the chance to capture SAEs. Second, the geographical representativeness of our cohort remained suboptimal, despite the contribution of the national scientific society, formally inviting all the active hyperbaric oxygen centres to join the project. Indeed, centres that did not participate may differ substantially in case mix and organizational models. A major limitation was the low number of private centres, that may have been encountered barriers to participation such as low availability of human resources and administrative issues. Notably, private institutions may have different proportion of indications to treatment and different proportion of urgent and elective cases and would have enriched the included cohort. Additionally, seasonality of some indications to treatments (e.g. decompression illness) may also have limited the external validity of our cohort. Allowing centres to start enrollment at a convenient start date was intended to maximize case capture and ensure adequate representation of conditions typically managed at each site, but staggered enrolment may have influenced the distribution of cases observed, reducing external validity of our results.

In addition, excluding patients already receiving hyperbaric oxygen treatment for chronic conditions may have limited validity of our data regarding the centres real workload.

Importantly, the assessment of clinical resolution at 30-day follow-up after last treatment cycle was based on non-standardized clinical judgment, which reasonably varied across centres and indications, introducing measurement bias. The lack of standardized and validated outcome measures was a key limitation for this secondary outcome.

The assessment was performed during a follow-up visit or a follow-up phone call, with no pre-specified indication-specific criteria to define resolution. Thus, the clinical benefit

perceived by the patients might not indicate disease resolution that may have needed comprehensive imaging evaluation or other disease specific criteria to be established. Moreover, the follow-up occurred 30 days after the completion of the cycles prescribed, that may have varied in number across centres and indications.

Moreover, 30-day can be considered a relatively short follow-up timepoint, not fully able to capture long-term outcomes. For example, delayed neurological sequelae (DNS), typically manifest 2–40 days after apparent recovery in patients with CO poisoning and our design may have sub optimally tracked such outcomes.

Finally, the lack of pre-specified criteria to define elective or urgent a treatment and different centres operational models (24/7 vs. weekday-only) further limited the external validity of our findings.

However, our study also has strengths. First, the feasibility of an unprecedented research network in the field, multicentre participation and the inclusion of a relatively large and heterogeneous patient population. Plus, the prospectively collected data, the standardized electronic case report form adopted and the availability of data on a short-term follow-up. These aspects enhanced the external validity of the findings and contributed meaningful real-world data to a field where contemporary observational evidence remains limited.

Additionally, representativeness of the participating centres was informative for the purposes of the study, given the presence of institutions from all the geographical macroareas of Italy and the capacity to capture almost all the current indications to

treatment. Moreover, the inclusion of new cases only allowed us to prospectively collect data on indications, characteristics of the treatments and adverse events, usually retrospectively unavailable. Overall, the real-world design offered insights for future research and organizational policies.

CONCLUSIONS

Hyperbaric oxygen therapy in Italy seems to be adopted in line with current national and international guidelines, in terms of indications and modalities. The most frequent indications were sudden hearing loss, CO poisoning and soft tissue infections. A low prevalence of other indications was registered, including rare off-label indications.

Treatments had similar characteristics across the centres, with heterogeneity mainly regarding the number of sessions per patients.

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List of abbreviations

CO, carbon monoxide

DNS, delayed neurological sequelae

HBOT, hyperbaric oxygen therapy

RCT, randomized controlled trial

SAE, serious adverse event

Declarations

Human Ethics and Consent to Participate

Human Ethics Committee approval was obtained prior to study conduction (first approval by EC Palermo 1 date: 08/04/2024). Written informed consent was obtained by all the participants to participate to the study according to national regulations.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

MI and LM are members of the Executive Board of SIAARTI. AC is Editor in Chief of JAACC. All the other authors declare no competing interest.

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Authors' contributions

MI, AC, FR, CS conception of the work; MI, LM, AN, GS, MN, SS, VT, FR, CS, EB, AG, AC: design of the work methodology, data collection, interpretation of data; MI, LMan, DM, AC: data analysis; MI and AC drafted the work; MI, LM, AN, LMan, GS, MN, SS, VT, SB, LGVS, CF, LC, ANC, LT, FF, AG, FR, CS, EB, DM, AG, AC: data collection, substantial revision of the manuscript. All authors have approved the submitted version (and any substantially modified version that involves the author's contribution to the study) and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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SIAARTI Study Group

Vincenzo Benenati, Emanuele Corallo, Ilde Covino, Sarah Di Miceli, Fabio Favorito, Andrea Galvani, Carmelo Gigliuto, Alessandro Marchignoli, Anna Teresa Mazzeo, Francesca Moretto, Dario Nicosia, Carolina Nuzzo, David Pacchioli, Daniela Maria Palma, Barbara Pifferi, Gabriele Presti, Nadia Stagni, Rosanna Vaschetto