Emerging Indications for Hyperbaric Oxygen Treatment: A Registry Cohort Study

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Abstract

Background: Hyperbaric oxygen (HBO2) treatment is used across a range of medical specialties for a variety of applications, particularly where hypoxia and inflammation are important factors. HBO2 may be useful for new indications not currently approved by the Undersea and Hyperbaric Medical Society (UHMS) because of its hypoxia-relieving effects. Identifying these new applications for HBO2 is difficult because individual centers may only treat a few cases and not track outcomes in a consistent way. The web-based International Multicenter Registry for Hyperbaric Oxygen Therapy captures outcomes data for patients treated with hyperbaric oxygen (HBO2) therapy. These data can then be used to identify new applications for HBO2.

Objective: Identify cases where HBO2 is used for indications other than the current UHMS approved indications and present existing outcome data for them.

Methods: This is a descriptive study based on a web-based, multi-center, international, registry of patients treated with HBO2. Centers agree to collect data on all patients treated using standard outcome measures and send deidentified data from individual centers to the central registry. HBO2 treatment programs in the United States, United Kingdom, and Australia participated. Demographic, outcome, complication, and treatment data, including pre- and post-treatment quality of life questionnaires (EQ-5D-5L) were collected on individuals referred for HBO2 treatment.

Results: Out of 7545 patient entries, 354 individuals were treated for 44 emerging indications. Post-acute COVID syndrome (PACS) (148), ulcerative colitis (45), and Crohn's disease (34), accounted for 64% of total cases. Calciphylaxis (18) and peripheral-vascular-disease related wounds (11) accounted for a further 8%. PACS patients reported significant improvement on the Neurobehavioral Symptom Inventory. Crohn's disease patients reported significantly improved fistula drainage and ulcerative colitis patients reported lower scores on a bowel questionnaire examining frequency, blood, pain, and urgency. A subset of calciphylaxis patients also improved.

Conclusions: HBO2 is being used for a wide range of possible applications across various medical specialties for its hypoxia-relieving and anti-inflammatory effects. Results show significant improvements in patient reported outcomes for inflammatory bowel disease and PACS. Clinical Trial: DERR1-10.2196/18857

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Emerging Indications for Hyperbaric Oxygen Treatment: A Registry Cohort Study

Abstract

Background: Hyperbaric oxygen (HBO2) treatment is used across a range of medical specialties for a variety of applications, particularly where hypoxia and inflammation are important contributors. HBO2 may be useful for new indications not currently approved by the Undersea and Hyperbaric Medical Society (UHMS) because of its hypoxia-relieving and anti-inflammatory effects. Identifying these new applications for HBO2 is difficult because individual centers may only treat a few cases and not track outcomes consistently. The web-based International Multicenter Registry for Hyperbaric Oxygen Therapy captures prospective outcomes data for patients treated with hyperbaric oxygen (HBO2) therapy. These data can then be used to identify new potential applications for HBO2, which has relevance for a range of medical specialties.

Objective: Although hyperbaric medicine has established indications, new ones continue to emerge. One objective of this registry study is to identify cases where HBO2 has been used for conditions falling outside of current UHMS-approved indications and present outcomes data for them.

Methods: This is a descriptive study based on a web-based, multi-center, international, registry of patients treated with HBO2. Centers agree to collect data on all patients treated using standard outcome measures and send deidentified data from individual centers to the central registry. HBO2 treatment programs in the United States, United Kingdom, and Australia participate. Demographic, outcome, complication, and treatment data, including pre- and post-treatment quality of life questionnaires (EQ-5D-5L) are collected on individuals referred for HBO2 treatment.

Results: Out of 9726 patient entries, 378 individuals were treated for 45 emerging indications. Post-acute sequelae of COVID (PASC) (149/378 40%), ulcerative colitis (47/378 12.4%), and Crohn's disease (40/378 11%), accounted for 62% of total cases. Calciphylaxis (20/378 5.3%), frostbite (18/378 4.8%), and peripheral-vascular-disease related wounds (12/378 3.2%) accounted for a further 13.2%. PASC patients reported significant improvement on the Neurobehavioral Symptom Inventory (NSI pre 30.6, NSI post 14.4, $p<0.001$). Crohn's disease patients reported significantly improved quality of life (EQ-5D pre 53.8, post 68.8) and 5 reported closing a fistula. Ulcerative colitis patients showed strong trends toward improved quality of life and lower reported lower scores on a bowel questionnaire examining frequency, blood, pain, and urgency. A subset of calciphylaxis and arterial ulcer patients also reported improvement.

Conclusions: HBO2 is being used for a wide range of possible applications across various medical specialties for its hypoxia-relieving and anti-inflammatory effects. Results show statistically significant improvements in patient-reported outcomes for inflammatory bowel disease and PASC. HBO2 is also being used for frostbite, pyoderma gangrenosum, pterygium, hypospadias repair, and facial filler procedures. Other indications show evidence for improvement and the case series for all indications is growing in the registry.

Trial Registration: DERR1-10.2196/18857

Keywords: Hyperbaric oxygen; inflammatory bowel disease; calciphylaxis, post-acute sequelae of COVID-19, infected implanted hardware, hypospadias, frostbite, facial filler, pyoderma gangrenosum.

Introduction

Hypoxia and inflammation are part of the pathophysiology for various conditions across a range of medical sub-specialties. One approach to relieving hypoxia and reducing inflammation is the use of

hyperbaric oxygen (HBO2). HBO2 is 100% oxygen delivered at pressures greater that 1.4 atmospheres absolute (ATA) within a pressurized chamber. Typically, pressures of 2.0 ATA or greater are used. HBO2 treatments greatly increase the amount of oxygen dissolved in plasma and tissue during the treatment and are very effective for relieving hypoxia. The high levels of oxygen in tissue lead to a variety of biochemical effects including reduced inflammation and the release of stem/progenitor cells from the bone marrow [1, 2] leading to its application in a several conditions, often in cases when standard treatment is not effective.

Currently, the Undersea and Hyperbaric Medical Society (UHMS) has identified 15 conditions where HBO2 can be considered an approved treatment [3]. These range from “caisson disease” (decompression illness) where the combination of increased pressure, relief of hypoxia, and reduced inflammation from HBO2 help combat the impaired circulation and endothelial damage caused by bubbles [4], to radiation injury where the pulses of oxygen promote angiogenesis and wound healing [3]. Because of HBO2’s effects on hypoxia and inflammation, more medical diagnoses likely exist that can benefit from HBO2. HBO2, however, is typically given in long courses (20-40 treatments) and most centers see only a limited number of patients. As a result, gathering outcomes data on HBO2 treatment has been limited and often only case reports or small case series are available to support its use. Also, practice patterns differ across centers and some centers may use HBO2 successfully for an indication that other centers may not consider it for. To gather more data on HBO2 applications, outcomes data from multiple centers need to be combined, but until 2011, no major academic registry existed to record treated cases and to track outcomes [5, 6].

The International Registry for Hyperbaric Oxygen Treatment was formed to gather consistent outcome data from multiple centers [5]. The registry’s goal is to improve the use of HBO2 through evidence-based medicine. The registry records all hyperbaric medicine cases seen at participating centers and includes data on demographics, outcomes, complications, treatment duration, treatment pressure, and quality of life (QOL), among other markers. The registry started at the Dartmouth-Hitchcock Medical Center and Elliott Hospital in 2011, but expanded significantly in 2020, when the number and geographic distribution of participating centers grew. Thirty-two centers are entering data as of May 2024. The registry includes centers in the United States, United Kingdom, and Australia (Table 1) and the data are used in publications about the use of HBO2 [6-8].

An important outcome from the registry is identifying emerging medical indications for HBO2 treatment. Particularly at academic centers, unique or challenging cases where hypoxia, inflammation, or both are considerations are referred for HBO2 treatment. The types of cases referred, and the outcomes from them, can indicate which new indications may need further study in controlled trials. This information can also support the use of HBO2 for individual conditions when other treatments are not effective. Since registry inception, 378 cases have been recorded where treatment was given for a condition falling outside of the current 14 UHMS-approved indications. The goal of this analysis is to: a) quantify which non-UHMS-approved indications are being treated at registry centers, and b) provide outcomes for indications where sufficient cases exist. This analysis is important to: a) identify indications deserving of further research, b) inform both hyperbaric and other practitioners on new and emerging uses of HBO2, and c) identify potential applications of HBO2 treatment across various medical and surgical specialties for challenging and difficult cases.

Methods

To guide the presentation of data in this report, the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement was used [9]. RECORD was created as an extension to the Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) statement to address reporting items specific to observational studies using routinely collected health data such as registries. The checklist is included as supplemental material.

Registry design and data collection

The structure of the web-based International Multicenter Registry for Hyperbaric Oxygen Therapy has been described previously [5]. Briefly, the registry is composed of hyperbaric centers that agree to follow the registry consortium agreement when becoming a member. Every site obtained IRB approval and gathered informed consent in agreement with their IRB approval. Sites either obtain institutional Review Board (IRB) approval from their own IRB or establish a reliance agreement with the IRB Dartmouth College. Informed consent differs across centers with some centers having an approved waiver of consent and others requiring a separate consent from the hyperbaric treatment consent for all patients. Data are de-identified when they are sent to the data coordinating center. Participants do not receive compensation.

All centers use a free database application (REDCap- Research Electronic Data Capture) for data entry. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Registry data from each center are anonymized and collated every quarter at the coordinating center (Dartmouth) and are available to all users for research purposes [10, 11].

Data are collected within a week of beginning and ending HBO2 treatment. All patients have relevant demographic data recorded (age, biological sex, race). Yes/No questions are asked about any history of prior HBO2 treatment, prior seizures, or current pregnancy. Patients are asked about diabetes (whether diet-controlled, on oral medications, or on insulin) and about any current or prior smoking history or other nicotine use. At the end of treatment, the number of treatments given is recorded along with any treatment complications that may have occurred.

Several patient-reported outcome questionnaires are used. All the questionnaires are maintained on the registry website. Any updates to documents are thus easily distributed to the centers that all have access. Patients are asked to complete the EuroQol EQ-5D-5L Quality of Life (QOL) questionnaire at the beginning and end of treatment [12]. This questionnaire asks about health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels and the answers to the five questions are combined into one composite score or index. Scores range from −0.59 to 1, where 1 is the best possible reported health. Overall health is also rated on a 0–100 hash-marked, vertical visual analogue scale (EQ-VAS). The EQ-5D-5L questionnaire is a copyrighted evidence-based assessment of health and has been registered for registry use. It has been incorporated into all entries collected since 2019 to evaluate overall health pre- and post- HBO2. Patients treated before then do not have results for this questionnaire.

Depending on indication, additional questionnaires (e.g., urinary distress inventory for radiation cystitis, EORTC QLQ-H&N35 for head/neck cancer, etc.) are administered in accordance with registry protocols. For Crohn’s disease patients, the perianal Crohn’s symptom index is completed which asks about number of fistulas, fistula drainage, rectal drainage, bowel movement frequency, and the use of motility agents. Administration of this questionnaire began in 2019 and is included as Appendix 1. Ulcerative colitis patients receive a questionnaire that asks about bowel movement frequency during the night and day, blood in the stool, urgency, and pain. The frequency, blood, urgency, and pain factors are combined into an overall score that ranges from 0 (no symptoms) to 17

(maximum symptoms) to characterize severity of symptoms. Administration of this questionnaire also started in 2019 and is included as Appendix 2. Because the Crohn's and ulcerative colitis questionnaires were added later in the registry's development patients treated before that time do not have results from these questionnaires.

Patients with head trauma and post-COVID symptoms are presented with the Neurobehavioral Symptom Inventory (NSI) [13]. The NSI has 22 questions designed to cover symptoms related to concussion. Patients rate the severity of common symptoms such as headache, fatigue, nausea, etc. on a scale ranging from 0 (none) to 4 (very severe) with the maximum total score of 88. Initially, this questionnaire was only administered to patients with CO poisoning but in 2022 this questionnaire was expanded to any brain-related condition (including those with the post-acute sequelae of COVID syndrome (PASC)). For frostbite, the users are presented with diagram of the hands and feet and they select the affected areas (Figure 1).

As the data are coded by indication, records are classified into one or more of the 15 approved UHMS indications or categorized as "Other". The design of this study was to focus on all those records where the indication was "Other" and to combine data for those indications. Data entries fitting into the "Other" category were isolated and subsequently further divided into subgroups for investigation in this study. Data were reviewed manually to determine if the record fit into one of the already recognized "Other" indications or if it was an indication that did not exist within the registry. For example, Crohn's disease is a selection on the "Other Indications" dropdown menu, however, this option was not always present in the registry. Previously, users would select "Other" and then enter Crohn's disease in a text box. So, these text entries were examined to ensure the cases were properly classified. Once the text had been identified, data were processed using MATLAB 2023a (The MathWorks Inc, Natick, MA), by implementation of text recognition algorithms to properly classify the reasons for treatment. These results were manually double-checked for accuracy using Microsoft Excel (Microsoft Corporation, Redmond, WA). The study size was determined by the number of entries for "Other" indications in the registry from registry inception in 2011 through May 2024.

Missing Data Reasons

Either pre or post treatment data were missing for a variety of reasons. For some of the questionnaires, data collection did not start until the registry had been underway for several years. This is true for the EQ-5D-5L, the Crohn's, ulcerative colitis, and NSI questionnaires. So, patients treated early in the registry do not have results for these questionnaires. In other cases, data are missing because the patient either discontinued treatment, was discharged from the hospital, or transferred to another facility and was not available for the final questionnaire. Some patients were too ill to complete the questionnaires.

Statistical Analysis

For those indications with sufficient responses (n=6 or more) and complete pre and post data for the variable in question, pre and post values were compared statistically. Questionnaire responses or rating scales where the answers were categories were analyzed using the sign test (e.g. EQ-5D-5L, NSI, bowel questionnaire). Otherwise, data were compared using the Wilcoxon signed-rank test (e.g., fistula number on the Crohn's symptom index). Individuals who were missing a pre or post value for a variable were not included in the primary analysis.

Treatment of Missing Data

The baseline characteristics of those with complete and incomplete Crohn's, ulcerative colitis, and PASC conditions were calculated and presented in the results. We conducted sensitivity analyses to tease out the potential impacts of the missing data as follows. Individuals who were missing EQ5D questionnaires but had other data in the registry indicating they had a positive response were given pre and post treatment values at the pre and post mean values of those with complete data. For the remainder, we used best, worse, and average case scenarios. In the best case, we assumed all those with missing data improved to the same degree on average as those with complete data. For the worse case we assumed all those with missing data worsened by the same average percentage that those with complete data improved. For the average case, we calculated the proportion of individuals with complete data that improved and applied that to the missing data. We took the view that sensitivity analyses were not appropriate when the number of cases with complete data was very small and we used 10 as the limit, accepting that this is an arbitrary limit.

Results

As of May 2024, 32 sites were actively entering data in the registry and 24 of these centers contributed to indications labeled "Other" (Table 1). 378 cases total were marked as having diagnoses not currently UHMS-approved and receiving at least one hyperbaric treatment. One center had an interest in PASC and contributed 141 out of 149 cases for that indication. Aside from PASC, ulcerative colitis (UC) was the most common condition (n=47), followed closely by Crohn's disease (n=40). Combined, inflammatory bowel disease (IBD, n=87) accounted for 23% of hyperbaric cases treated as "Other"(n=378). If combined with pouchitis (n=1) and pyoderma gangrenosum (n=7), which both are often associated with IBD, total IBD and related cases accounted for 25% cases treated (95 of 378). Of the remaining diagnoses treated, calciphylaxis, frostbite, and peripheral vascular disease ulcers each had 10 or more cases. There were 23 diagnoses with only a single case (Table 2). The result of this was a series of case cohorts and individual case studies gathered into a single database.

Table 1. Center totals for emerging indications contributing to the analysis

Center	Location	Total cases in registry	Total emerging indications
Alfred Health	Melbourne, AU	135	1
Avera McKennan Hospital	Sioux Falls, SD	310	10
Beverly Hospital	Beverly, MA	67	2
DDRC Healthcare	Plymouth, UK	109	4
Dartmouth-Hitchcock Medical Center	Lebanon, NH	1118	74
Duke University Medical Center	Raleigh, NC	319	4
James Paget University Hospital	Great Yarmouth, UK	47	4
Intermountain Medical Center	St. Murray, UT	495	10
Latter Day Saints Hospital	Salt Lake City, UT	283	2
Legacy Health Group	Portland, OR	645	12
LHM Healthcare	London, UK	131	6
Logan Regional Medical Center	Logan, UT	110	1
Mayo Clinic	Rochester, MN	947	11
Midlands Diving Chamber	Rugby, UK	171	152

Center	Location	Total cases in registry	Total emerging indications
Prince of Wales Hospital	Sydney, Australia	847	36
Spectrum Health	Grand Rapids, MI	409	6
St. George Regional Hospital	St. George, UT	310	5
St Richard's Hospital	Chichester, UK	15	4
University of California San Diego	San Diego, CA	385	12
University of Maryland Medical Center	Baltimore, MD	1260	29
University of Pennsylvania	Philadelphia, PA	223	1
Utah Valley Hospital	Provo, UT	450	6
Wesley Hyperbaric	Brisbane, Australia	233	4

Table 2. Summary of other indications. Some of the indications were case series with several cases, others were case reports of individual cases.

Indication	Total	Indication	Total
Post COVID syndrome	149	Chronic anal fissure	1
Ulcerative colitis	47	Vasculitic ulcer	1
Crohn’s disease	40	BK virus cystitis	1
Calciphylaxis	20	Levamisole vasculitis	1
Frostbite	18	Graft vs host disease	1
Peripheral vascular disease ulcer	12	Decubitus ulcer	1
Acute COVID-19	9	Greater trochanteric pain syndrome	1
Pyoderma gangrenosum	7	Rectovaginal fistula	1
Pterygium	7	Argon poisoning	1
Hypospadias	7	Pouchitis	1
Osteonecrosis/Avascular necrosis	6	Chemotherapy-related bladder ulcer	1
Head trauma	5	Post surgery in irradiated tissue	1
Infected implanted hardware	5	Recurrent perianal abscess	1
Pneumatosis intestinalis	4	Tinnitus	1
Facial filler	4	Clostridium enterocolitis	1
Ischemic bowel	3	Ligament/Cartilage injury	1
Raynaud’s syndrome	2	Branch retinal artery occlusion	1
Malignant otitis externa	2	Axonotmesis	1
Non arteritic anterior ischemic optic neuropathy	2	Non healing bowel anastomosis	1
Central retinal vein occlusion	2	Multiple sclerosis	1
Cyclophosphamide cystitis	2	Inclusion body myositis	1
Femoral head necrosis	2	Epidermolysis bullosa	1
Invasive fungal infection	1		

Inflammatory bowel disease and related conditions

Crohn's disease

The 40 Crohn's disease cases had a mean(SD) age of 37(13) years with 14 men and 26 women. The racial breakdown was White 28, Black 2, Asian 2, More than one race 1, and Missing 7. The median number of HBO2 treatments completed was 30. Within the Crohn's cases, 25 of the 40 had complete pre and post treatment data for the EQ-5D-5L Quality of Life measure. Seven patients were missing data due to being entered in the registry prior to adoption of the questionnaire. Three did not complete the pre-treatment questionnaire and an additional 5 did not complete the post-treatment questionnaire. Of the 3 with no pretreatment questionnaire, one transferred to another HBO2 center and one was reported to have improved. Of those 5 with a pre, but no post, questionnaire, one was improving but insurance would not approve additional treatments, one had closed a fistula and stopped treatment, and one was discharged from the hospital and could not continue as an outpatient. One completed 6 treatments and was feeling too sick to continue. Of those who completed the EQ-5D, 20 reported improvement and 5 were essentially unchanged ($p<0.001$) (Figure 2). The Crohn's patients with perianal Crohn's questionnaire results (18) reported a significant decrease in discharge from the fistulas after treatment (Figure 3). Five patients also reported a decrease in the number of fistulas.

For the sensitivity analysis, the 7 individuals with missing EQ5D questionnaires because they entered the registry prior to its initiation were slightly younger (32 vs. 37) with a similar total number of treatments (40 vs 37) and were considered to be missing at random. Of the remaining 8, 3 were reported to have improved elsewhere in the registry and so were 'given' values at the mean pre and post for those with data. One was reported to be too sick to continue so was assumed to have worsened by the same average percentage that others had improved (28%). For the remaining 4, the best, worse, and average case scenarios were used. The best case assumed the 4 individuals all improved on the EQ5D VAS by the average amount and the worst case assumed that they worsened by the same average percentage that others had improved (28%). For the average case, the same proportion of improvement for those with data (20/25 or 80%), was applied to the 4 cases (i.e. 3 improved and 1 worsened). These gave: best case 27/33=82% improved $p<0.001$; worst case 23/33=70% improved $p=0.001$; average case 26/33=79% improved $p<0.001$. If the 3 individuals missing EQ5D data, but were noted to improve, were assumed to have worsened instead, this would still have been statistically significant, ($p=0.04$)

For the fistula discharge data, there were 18 individuals with complete data. For the sensitivity analysis, the 3 individuals who reported improvement elsewhere in the registry were treated the same as the others with missing data. The best, worst and average case analyses showed: 25/33=76% improved, $p<0.001$; 10/33=30% improved, $p=0.33$; 18/33=55% improved, $p=0.08$, respectively.

Ulcerative colitis

The 47 ulcerative colitis cases had a mean(SD) age of 41(20.5) with 24 women and 23 men. The racial breakdown was White 40, Black 2, Asian 1, Refused 1, and Missing 3. The median number of treatments was 5. Within the UC cases, 18 had complete EQ-5D-5L questionnaire data. Six were missing data due to being in the registry before the EQ-5D was adopted. Twelve had no pre-treatment questionnaire and an additional 10 had no post-treatment questionnaire. Of those with no pre-treatment questionnaire, one had cognitive impairment, one was unable to complete the form, two declined, one decided to stop treatment, one stopped due to an unrelated medical problem, and four stopped because they had improved. Among those with no post-treatment questionnaire despite having a pre-treatment result, 4 were discharged before completing the form, in 3 cases the patient

terminated treatment, and in an additional 3 treatment ended unexpectedly. The group without pre-treatment questionnaires tended to be older (mean=48 years) and receive more treatments (median=8.5). The group missing post-treatment questionnaires had a similar mean age (41) and median number of treatments (4.5) to the questionnaire group. In the 19 UC patients who completed the EQ5D, three had slightly decreased QOL scores while the majority had improvement (p=0.008) (Figure 4). The UC patients with questionnaire results also reported lower (better) scores on the bowel questionnaire (Figure 5). For the sensitivity analyses, the 4 UC cases that reported improvement were assumed to have improved by the mean of those with data. For the remainder and best, worst, and average case were: 38/41=93% improved, p<0.001; 19/41=46% improved, p=0.76; 31/41=76% improved, p=0.002 respectively.

There were 7 individuals with pyoderma gangrenosum, 6 women and 1 man with a mean(SD) age of 46(20.6). The racial breakdown was White 5, Black 1, and Asian 1. The median number of treatments was 26. Data for these cases are limited because standard wound measures for these cases were implemented late in the registry. Only 2 cases had EQ-5D measurements. Two cases were entered in the registry prior to beginning EQ-5D assessments, 2 had no pre-treatment value, and 1 had no post treatment value. Three had subjective data on improvement and those 3 were reported to improve. One patient stopped due to an unrelated medical problem, and another decided to stop after 7 treatments. The registry also includes one patient with pouchitis who improved.

Calciphylaxis

Calciphylaxis was the fourth most common “other” diagnosis (n=20) (Table 3). The mean(SD) age was 61(15.9) with 12 women and 8 men. The racial breakdown was White 15, Black 3, Refused 1, and Missing 1. The median number of treatments was 27.5. Only three patients had complete QOL data. Five individuals did not have EQ-5D data because they were treated prior to the EQ-5D being in the registry. Six had no pre-treatment questionnaire and 6 had no post-treatment questionnaire. Four patients discontinued treatment as they were too sick to continue, and two of these patients died. Two patients healed their wounds and five showed notable improvement. Of those who improved, the average number of treatment sessions was 35. The average number of hyperbaric treatments of the remaining cases was 21. Sensitivity analyses were not used because the most useful outcome for this condition is improvement vs. no improvement because of the high mortality. Many of the patients missing data either died or were seriously ill.

Table 3. Outcomes for the patients with calciphylaxis.

Total HBO2	Original Size in cm (LxWxD)	% decrease length	% decrease width	% decrease depth	EQ5D VAS Pre	EQ5D VAS Post	Missing EQ5D Reason	Notes on outcome
Improved								
8	12x10x4	33.3	30	75			Prior to EQ5D in registry	Patient decided to stop; better
32							Not done	Improved
29	7x1x0.5	98.6	80	100			Prior to EQ5D in registry	Wounds healed
18	11.3x5.4x2.5				50	40		Wounds improving; stopped due to other health issues
40	45x15x25	8.9	30	0	30		Patient unable to return form	Despite size, considerably improved (granulation)
60	3.7x5x0.1	67.6	-22	10	87	92		Wounds improved
39	4.3x0.8x0.1	100	100	100			Prior to EQ5D in registry	Transferred to other hospital, wounds healed
48	L 1.9x5.0x2.2	58	40	82			Prior to EQ5D in	Wounds mildly

Total HBO2	Original Size in cm (LxWxD)	% decrease length	% decrease width	% decrease depth	EQ5D VAS Pre	EQ5D VAS Post	Missing EQ5D Reason	Notes on outcome
	R 2.0x9.5x2.2	40	26	82			registry	improved
40					30	80		Improvement in quality of life
Not improved								
17							Unable	No change (wound care)
11	5x2.5x1	-500	-500	-100	10		Patient did not return	Worsening/Poor nutrition- stopped as futile
21					30		Unable to complete	Worsening. Too sick to continue
9					10		Stopped care	Patient decided to stop; claustrophobia noted
21	110x100x5						Unable	No change
26	7.1x4.9x3.5				50		Patient died	Transferred from outside hospital. Died
3	8x5x2						Declined	Patient decided to stop (non-medical reason)
10							Prior to EQ5D in registry	Developed resp illness, died
40	6x5x0	0	-10				Not done	Wounds unchanged per measurements
40							Declined	No improvement
40					40		Not done	No outcomes documented

Frostbite

Frostbite was the fifth most common “other” diagnosis with 18 patients. The mean(SD) age was 49 (13.7) years with 17 men and 1 woman. The racial breakdown was White 12, American Indian/Alaska Native 2, Other 2, Black 1, and Missing 1. The median number of treatments was 9. One individual did not have EQ-5D data because treatment occurred prior to the EQ-5D being in the registry. Six had no pre-treatment questionnaire and 6 had no post-treatment questionnaire. For 2 the questionnaire was not done for unspecified reasons, 3 either left treatment or refused treatment before completing the questionnaire, 1 had a language barrier, and 1 was not done due to inadequate staffing. For the 11 patients who had complete EQ5D VAS data there was a significant improvement (48.2 pre to 67.5 post, 82% improved, p=0.02). For the sensitivity analyses, the best, worst, and average cases were: 16/18=89% improved, p<0.001; 9/18=50% improved, p=1.0; 15/18=83% improved, p=0.002 respectively.

Table 4. Outcomes for patients treated for frostbite. The frostbite classification scale is 1=First degree, 2=Second degree, 3=Third degree, 4=Fourth degree (includes necrosis)

Total HBOT	EQ5D VAS Pre	EQ5D VAS Post	EQ5D score pre	EQ5D score post	Frostbite classification	Missing EQ5D Reason	Notes on outcome
Improved							
7	10	60	0.16	0.084	3		Improved, but had amputations
9	30	80	0.39	0.64	2		No amputations, improved
10	10		0.51		2	Not done	No amputations
4	85	95	0.33	0.44	4		Initial bilateral transmetarsal amputations, subsequently improved
27	80	95				Only VAS	Had a skin graft
9	30	75	0.69	0.27	3		No amputations, good healing,
10	45	48	0.53	0.37	2		Wounds stabilized
7	50	50	0.812	1	2		No amputations, wounds improved
10	80	50	0.40	0.42	2		Partial improvement, delay in HBO2 due to detox
7	50	70	0.41	0.80	2		No amputations, wounds improved

Total HBOT	EQ5D VAS Pre	EQ5D VAS Post	EQ5D score pre	EQ5D score post	Frostbite classification	Missing EQ5D Reason	Notes on outcome
9	50	70	0.82	0.82	2		Wounds improved
10	20	50	0.06	0.26	3		
Not improved/insufficient data							
30					2	Prior to EQ5D in registry	Frostbite of hands, insufficient outcome data entered
15	0		-0.074		3	Had amputations, left treatment	Amputations on right and left foot. Homeless/drug use
4						Not done	Bilateral below the knee amputations
4					3	Language barrier	Behavioral issues/refused treatment. Bilateral below the knee amputations.
6						Staffing	Psychiatric issues/refused treatment
2	75		0.58			Did not return	Left treatment

Peripheral vascular disease related wounds

The sixth most-commonly treated diagnosis was peripheral vascular disease related wounds (Table 5). The mean(SD) age was 63(19.1) years with 8 men and 4 women. The racial breakdown was White 8, Black 2, and Missing 2. The median number of treatments was 19.5. Twelve cases were recorded, all involving arterial disease but some also with concurrent venous disease. All wounds involved the lower extremities. Of those patients who had 20 or more HBO2 sessions, 5 of 6 improved with the remaining one lacking enough data to make a conclusion. The remaining 6 cases had 15 or fewer sessions. Four of these were worse, with two not having sufficient data recorded. The main outcome recorded was improved vs. not improved/insufficient data, there were insufficient EQ5D data to do a sensitivity analysis.

Table 5. Outcome for patients with peripheral vascular disease.

Total HBOT	% decrease length	% decrease width	% decrease depth	EQ5D VAS Pre	EQ5D VAS Post	EQ5D score pre	EQ5D score post	Missing EQ5D Reason	Notes on outcome
Improved									
30	71.4	50	0		60			Not given pre	Improved/Healing
30	59.7	47.3	0	85	90	0.83	1.0		Improved/Healing
30	66.7	83.3	83.3	70	70	0.68	0.62		Improved/Healing
24	100	100	100					Unable	Resolved/Healed
60	56	67	100	100	90	0.42	0.80		Stump wound closed
No improvement/insufficient data									
6								Unable	Limited information
10								Prior to EQ5D in registry	Worse
15				75		0.88		Too sick to complete	Too sick to continue
1								Left treatment	Patient decided to stop
1								Left treatment	Patient decided to stop
9								Left treatment	Transferred to nursing facility
40								Not done	Had a skin graft

Pterygium surgery and facial filler injections

One particularly interesting application of HBO2 was for post-operative healing from pterygium surgery (Table 6). The mean(SD) age was 47 (18.1) years with 6 men and 1 woman all with “White” as the racial classification. All cases came from a single center and were treated with five sessions each. One case had an unchanged QOL assessment before and after treatment but had no noted complications via notes after surgery, and one had worse QOL Visual Analog Scale (VAS) scores after treatment (85 pre to 75 post) although was noted to have uneventful recovery after surgery. The

remainder all showed improvement in their QOL scores with the overall median EQ-5D-5L VAS score increasing from 82.5 to 97.5, although this was not statistically significant.

Table 6. Outcomes for patients with pterygium and facial filler injections

Total HBOT	EQ5D VAS Pre	EQ5D VAS Post	EQ5D score pre	EQ5D score post	Missing EQ5D Reason	Notes on outcome
Pterygium surgery						
5	85	75	1	0.83		Uneventful
5	90	90	0.88	1		No post-op problems
5	90	100	0.86	1		No post op problems
5	80	100	0.83	1		
5	70	100	0.88	1		
5	70	95	0.82	1		
5					Not done	
Facial filler injection						
6					Unable	Improved
1	95		0.81		Post ictal	Had seizure
5	75	85	0.82	1		Improvement in bruising/ischemia
5	95				Not done	Necrosis improved with HBOT

HBO2 was also used for complications due to the use of facial fillers (Table 6). The mean(SD) age was 46 (14.5) years. All were women all with “White” as the racial classification for 2 and for 2 the racial classification was missing. Two of four cases in the registry occurred after use of Radiesse, a calcium hydroxylapatite filler, while the other two were unspecified. Of the four cases recorded, all were treated in a multiplace chamber and three showed improvement with two stopping prescribed treatment sessions early due to recovery. Both that stopped early were on a twice daily schedule with one at 2.0 ATA and another at 2.4 ATA. One did not have a result listed other than stopping early secondary to a seizure as a complication, but this patient was taken to 2.8 ATA, which increases seizure risk. The final case was treated at 2.4 ATA daily, completing the prescribed 5 cases with improvement. All four cases were treated within one day of referral.

Non-radiation related osteonecrosis

Six cases of non-radiation related osteonecrosis were treated (Table 7). The mean(SD) age was 58(17.1) years with 3 men and 3 women. The racial breakdown was White 4, More than one race 1, and Missing 1. The median number of treatments was 30. In general, these patients received long treatment courses. The improvements in QOL seen in most patients suggest the treatment was generally successful.

Infected implanted hardware

Infected hardware was treated in five patients. The mean(SD) age was 49(9.6) years with 1 man and 4 women. Two were white and 2 were missing a racial classification. Two cases had knee hardware infection and two cases had spinal hardware infection. All were prescribed HBO2 at 2.4 ATA for 10 to 40 treatments, but none completed more than 30% of their course for various reasons, including patient decision, transfer to a different facility, and significant visual disturbances. None of these patients had pre- and post- QOL measurements.

Table 7. Outcomes for patients with non-radiation related osteonecrosis. Currently, no detailed outcome measures specific to osteonecrosis exist in the registry. The increase in the EQ5D suggests improvement.

Total HBOT	Anatomic Location	EQ5D VAS Pre	EQ5D VAS Post	EQ5D score pre	EQ5D score post	Missing EQ5D reason	Notes on outcome
20	Knee					Not asked	
60	Ankle	30	80	0.73	0.83		
20	Lower leg	60	80	0.15	0.54		Uneventful course
60	Left knee	60	65			Only VAS	
40	Jaw	35	50	0.23	0.57		Uneventful course
3	Sinuses/Palate	50		0.76		Transferred before completion	Had lymphoma on bone biopsy, HBO2 suspended

Hypospadias

HBO2 was also used in the setting of hypospadias repair. Repairs of hypospadias can lead to failed grafts with scarring, fistulas, strictures, and potential deformities [14, 15]. Some centers use HBO2 before and after the repair to improve graft and surgical outcomes. Seven cases were entered in the registry. The mean(SD) age was 3.7(2.6) years. The racial breakdown was White 3, Asian 2, Black 1, and Missing 1. For 5 the graft was preserved and viable, while for 1 the graft was preserved and partially viable. One was missing outcome data.

Post acute sequalae of COVID-19 (PASC)

A new application of HBO2 was for PASC. All but 8 of the 149 cases were reported by a single center, which has an interest in treating PASC with HBO2 [16]. Complete pre and post HBO2 NSI data were available on 127 patients (Figure 6). The NSI showed a significant improvement (NSI pre 30.6, NSI post 14.4, $p<0.001$). Complete EQ5D data were available on 55 individuals. The EQ5D VAS also improved significantly (33.6 pre to 64.1 post, $p<0.001$). The group included 80 women and 69 men (total n=149); 91.9% of patients were white, 4.7% Asian, 1.4% more than one race, and 0.7% black. The median number of HBO2 treatments was 15. In the sensitivity analyses, the best, worst, and average cases for the NSI were: 133/149=89% improved, $p<0.001$; 111/149=74% improved, $p<0.001$; 131/149=88% improved, $p<0.001$ respectively. For the EQ5D the best, worst, and average cases were: 142/149=95% improved, $p<0.001$; 49/149=33% improved, p=N.S. for improvement (most worsened); 130/149=87% improved, $p<0.001$ respectively.

Other diagnoses

For the other diagnoses, one group of indications were related to relief of hypoxia (e.g., ischemic bowel, Raynaud's syndrome, non-arteritic anterior ischemic optic neuropathy, central retinal vein occlusion, femoral head necrosis, branch retinal artery occlusion, vasculitic ulcer). The data on chronic anal fissures and Raynaud's add to existing case series for these conditions [17, 18]. Several cases focused on the treatment of cystitis (e.g., Human polyomavirus 1 (BK) virus cystitis, cyclophosphamide cystitis) likely motivated by the use of HBO2 for radiation cystitis treatment [7]. Not enough information exists to come to conclusions about effectiveness for these individual cases, but this likely will change as the registry matures.

Discussion

Principal Results

The registry is showing how HBO2 is being used across a range of medical specialties for indications where hypoxia or inflammation or both are significant factors. The emerging diagnosis treated most across the registry centers was inflammatory bowel disease (IBD) - primarily UC and Crohn's

disease. For Crohn's disease, there were sufficient entries to show statistically significant patient-reported improvement that remained significant even with the worst-case scenario sensitivity analysis. Overall, the newly described PASC was the most commonly treated diagnosis in this cohort although the results were predominantly from a single center. The patient-reported results showed improvement, which supports the need for further work in this area. The top five indications also included calciphylaxis and frostbite, which are both conditions where hypoxia is a significant consideration and where existing treatments are often inadequate.

The results also showed indications that were concentrated at particular centers, such as the use of HBO2 after complications for facial filler injections or to improve outcomes with pterygium surgery. The number of patients for each of these indications is limited but indicates that they could be studied in more detail to determine whether this approach should be adopted more widely at other centers.

Comparison to prior work

Inflammatory bowel disease

Several recent reviews have also concluded that hyperbaric oxygen could be useful for inflammatory bowel disease [19-24]. The registry data on Crohn's disease support other studies showing improvement with HBO2 [19, 25-29]. For fistulizing Crohn's disease, a prospective trial has shown reduced disease activity, reduced drainage, and clinical remission when HBO2 is used in refractory cases [26][7]. The improvement in the registry Crohn's cases is noteworthy because Crohn's disease is not currently an UHMS-approved indication for HBO2 and so patients are almost always referred because standard treatments have not been successful. The patients reported significant improvement in quality of life and reduced fistula and rectal discharge. Five patients closed fistulas. The quality-of-life results were significant even with the worst-case approach to the sensitivity analysis. The fact that 5 patients were able to close fistulas is significant because these were likely refractory patients. Taken together the results add to a growing set of case series and case studies that show improvement in difficult Crohn's cases and support the need for large scale trials.

For ulcerative colitis, HBO2 therapy studies have shown clinical remission, avoidance of colectomy or progression to second line therapy in a sham-controlled, randomized trial [30]. A follow-on phase 2B trial examined the dosing strategies and concluded that five sessions were superior to three for a UC flare [31][6]. Typically, HBO_2 is used adjunctively in ulcerative colitis with other treatments (steroids, biologic agents, etc.) although in one case study, HBO_2 was used successfully as monotherapy for ulcerative colitis in an individual who had contraindications to most standard treatments [32]. HBO_2 can be particularly useful in situations where the individual cannot receive standard treatment due to allergy, antibodies, shingles, or other reasons. The most common application of HBO2 in inflammatory bowel disease are patients admitted for an acute ulcerative colitis flare who are at risk for colectomy or cannot receive steroids or biologic agents or where there is a delay in being able to start those agents [30, 31]. Also, patients admitted for an acute ulcerative colitis flare who need a bridge between when IV steroids are begun and when biologic agents (i.e., infliximab) start to have an effect may benefit from HBO2. These registry results support the idea that HBO2 can be useful in ulcerative colitis but should be interpreted with caution. Many of the patients were hospitalized for treatment and were receiving intravenous steroids and other interventions. So, while the reports of improvement are encouraging, separating the effect of HBO2 from the effects of standard treatment is not possible in this dataset. Also, the fact that one center (Dartmouth-Hitchcock) accounted for many of the treated cases (roughly 75%) and had been involved in an ulcerative colitis clinical trial, may overrepresent the interest in UC across the registry centers. Also, the quality-of-life and bowel questionnaire results were not significant in the worst-

case of the sensitivity analysis. Randomized, controlled trials are needed to determine definitively if HBO2 improves upon standard care.

In addition to UC and Crohn's, IBD-related conditions where hyperbaric treatment could be applied include pouchitis, non-healing ileal pouch-anal anastomoses, and pyoderma gangrenosum (PG) [33-37]. Two published case series and a case report show relief of symptoms and decreased disease activity in pouchitis [33, 34, 38][8-10]. Case series and case studies also show reduced wound size in pyoderma gangrenosum [39][11]. The results from the present study align with these conclusions, but the registry results are descriptive and do not include a control group for comparison (as is true for most case reports and case series).

The IBD results support the idea that HBO2 could be considered in ulcerative colitis flares when standard therapy, such as steroids and biologics, is inadequate or not possible. Similarly, it could be useful in fistulizing perineal Crohn's disease refractory to medical and surgical treatments. Pouchitis that has not responded to antibiotics and immunomodulators as standard therapy and pyoderma gangrenosum refractory to steroids and immunologics are also potential applications of HBO2. IBD may be a disease process that should be evaluated as an UHMS-approved indication for HBO2 as accumulating evidence shows promising results.

Calciphylaxis

Calciphylaxis was the fourth most treated diagnosis. Calcification of small blood vessels leads to hypoxic, painful wounds which led to the use of HBO2 in these patients. No randomized control trials exist to guide the use of possible calciphylaxis interventions. Such trials would likely be very difficult to carry out because the disease is rare and disease severity varies widely. Also, calciphylaxis has a very high mortality. Most patients with calciphylaxis have end-stage renal disease (ESRD) and the 1-year mortality for those with ESRD and calciphylaxis is 45-80%. One-year mortality is less but still significant for those without ESRD (25-45%) [40]. Based on studies done to date, HBO2 has been recommended by subject matter experts to facilitate healing of recalcitrant calciphylactic ulcers after accounting for cost, availability, and patient tolerance of treatment [41]. Physiologically, HBO2 addresses the tissue hypoxia from the damage to small blood vessels characteristic of calciphylaxis. HBO2 greatly increases the amount of oxygen in circulation reaching hypoxic wounds, which promotes collagen formation and stimulates angiogenesis.

The results from the present study support what has been seen in prior work. A retrospective study of hyperbaric oxygen for calciphylaxis showed promising results; 34 patients received a full course of hyperbaric oxygen with 58% of patients improved and 32% completely healing their wounds [42]. In this prospective registry study 9/20 or 45% of patients improved. Like other studies, the registry results for calciphylaxis are mixed, which is not surprising considering the nature of this disease. Affected patients often have significant medical co-morbidities and the disease has a high morbidity and mortality rate secondary to sepsis. In this cohort, for example, 2 patients treated died of their disease and 2 others were too sick to continue. Nevertheless, there were several cases that improved significantly, and these successful cases had more sessions of therapy. Given the severe mortality and morbidity associated with the disease and difficult course of standard care, HBO2 is a treatment that has little risk with the potential for significant benefit. The results support previous positive case series and suggest that trials on HBO2 and calciphylaxis are needed and more research should be made to pursue calciphylaxis as a possible UHMS indication.

Frostbite

Frostbite cause hypoxia and necrosis in affected tissues and HBO2 has been considered as a potential therapy for many years. Kemper et al. summarized the literature on frostbite and HBO2 in 2014 [43]. In 2021, Magnan et al. published a multicenter prospective single-arm study of individuals with stage 3 or 4 frostbite who received HBO2 in addition to iloprost (n=28) [44]. The results were compared to a historical cohort that received iloprost alone (n=30). The results showed a significantly higher proportion of preserved frostbitten segments in the HBO2 plus iloprost group. The registry results support the results from these previous studies. Most individuals with EQ5D data reported an improved quality of life. In the sensitivity analysis this was significant in the best and average cases, but not the worst case. Determining whether HBO2 offers an additional benefit over standard treatment is not possible within the current registry design, but future expansion efforts could include trying to include registry centers without HBO2 who treat similar cases.

Peripheral vascular disease related wounds

Many of the emerging indications shared the underlying problem of tissue hypoxia. For the same reason that hyperbaric oxygen therapy would work in treating acute arterial insufficiency, it might assist healing of chronic peripheral arterial disease ulcers. A guideline from a wound care advisory panel for the treatment of arterial insufficiency ulcers recommends adjuvant HBO2 for patients with nonreconstructable anatomy or whose ulcer is not healing despite revascularization. The guideline also recommends determining if the hypoxia is reversible by hyperbaric oxygenation [45].

The registry cases show that some people did respond. Successful cases had at least 30 treatment sessions, while those with less than 15 sessions generally did not improve. Detailed information regarding each case is not available within the registry, so it is not known whether those who improved did so because they received more treatments or if they received more treatments because they had fewer co-morbidities or were showing early benefit. Also, whether the patients were screened using in-chamber transcutaenous oxygen measurements to document a local tissue increase in oxygen levels with hyperbaric oxygenation is not recorded. Patient selection is probably critical for deriving the most benefit from HBO2 in these patients because those with very severe hypoxia and vascular compromise may not respond. Further studies are needed to define how to select patients with peripheral vascular disease that might benefit from HBO2. Also, information on screening procedures used to select these patients for treatment should be added to the registry.

Other applications

An interesting application of HBO2, that was concentrated at one center, was the use of HBO2 after pterygium surgery. The recurrence rate of simple surgical excision can be as high as 40% but can be lowered to 16% with a conjunctival autograft procedure, although the recurrence rates are increased if the pterygium is already recurrent when the procedure is used [46]. The use of post-operative HBO2 treatment is based upon a prospective trial published in 2011 which showed low recurrence rates when pterygium patients underwent surgery with adjunctive HBO2 afterwards [47]. A short five-session HBO2 prescription was used. There were no complications noted with HBO2 in these cases and, importantly, no reported recurrences of pterygium. This local protocol that was used may be feasible to attempt at other centers, should collaboration with ophthalmology be obtained. At the very least, this is an interesting condition to further evaluate for using HBO2 as a successful adjunct treatment to standard therapy. Another indication that also focused on trying to improve outcomes after surgery is the use of HBO2 for individuals having hypospadias repairs. There were 7 individuals in the registry with this indication and all reported preservation of the graft, although in

one the graft was partially viable. These results are consistent with prior work [14]. Also, this application could be considered as an extension of the approved UHMS-indication of compromised flaps and grafts.

Facial filler complications present an emergency treatment opportunity well-suited for HBO2 and has been reported in several case reports [48-51]. This was identified in the registry cases as well. The experience of providers performing these outpatient facial filler procedures varies widely as does the ability and knowledge to address complications. With rising interest in aesthetic therapy, complications from these procedures are becoming more common. Facial fillers typically refer to hyaluronic acid fillers or particulate-based fillers, both of which are used for facial remodeling or tissue augmentation for cosmetic or reconstructive purposes. These injections can cause vascular obstruction and subsequent tissue ischemia; thus, the goal of treatment is to restore perfusion to the affected area. Although hyaluronic acid can be reversed with hyaluronidase, particulate injections such as calcium hydroxylapatite cannot easily be broken down and HBO2 may play an even greater role in these cases. Expert consensus protocols include HBO2 in treatment algorithms for these complications [52]. Like acute arterial ischemic cases, success likely hinges on the hyperbaric medicine consult occurring close to the initial injury. Early intervention must be encouraged, as with other UHMS-approved indications where acute ischemia is prominent such as central retinal artery occlusion or compromised flaps, because earlier intervention leads to improved results. Half of the cases recorded were treated on the same day as consult, although information on time duration from filler injection is not available. Ultimately, hyperbaric oxygen can support threatened tissue but cannot resuscitate dead tissue and aggressive intervention and resuscitation should be advocated. The information about the use of HBO2 for this indication needs to be available to other centers doing facial filler injections.

When implanted hardware is infected, the medical standard of care typically calls for hardware removal. Removal from certain areas of the body (e.g., brain, spine) can be difficult or involve complicated surgical intervention. In these instances, salvage of hardware has the lowest risk-to-benefit ratio or may be the only viable option [53]. Ridding foreign bodies of infection in vivo is notoriously difficult, which is why HBO2 was likely attempted in these cases. None of the patients treated completed their course of treatment, which may suggest these cases were refractory. The results suggest the registry should be revised to collect more detailed information about these cases.

The newly recognized PASC was treated multiple times in the registry. The anti-inflammatory effects of HBO2 are thought to be the mechanism of action underlying improvement. PASC is not yet completely understood, but likely results from a dysregulated inflammatory process within the brain [54]. In general, patients reported improvement with treatment. This matches reports coming from case reports and series, and from a randomized control trial out of Israel [55]. The results need to be interpreted with caution as placebo effects with HBO2 are common. Nevertheless, the data support further sham-controlled trials and suggest HBO2 could be used to treat other post-infectious syndromes in the future.

Many of the other individual case reports within the registry are for indications where hypoxia is believed to be a significant factor. Femoral head necrosis, for example, results from a compromised vascular supply and healing of chronic anal fissures is believed to be hampered by local hypoxia [56]. Ophthalmological conditions such as branch retinal artery occlusion, retinal vein occlusion, and non-arteritic anterior ischemic neuropathy involve hypoxia and a compromised blood supply. Raynaud’s syndrome and vasculitic ulcers are also characterized by local hypoxia. Currently, not enough data exist within the registry to draw conclusions about outcomes for these various conditions, but over time additional cases will accumulate.

The hyperbaric registry is still in its nascent stages. Greater adoption of the registry by the community will lead to more significant results. The cases highlighted in the report have identified additional data that should be recorded for some of these indications. The facial filler cases, for example, highlight the need for further information such as the time of injury to help determine the optimal timing for maximal HBO2 efficacy. Also, the facial filler cases should be documented in an identified category, as is done with indications like UC or Crohn's, rather than just marked as "Other". More specific outcome measures are needed for the non-radiation-related osteonecrosis cases. Also, long-term follow-up will be essential for infected hardware cases because the ultimate outcome may not be known until well after the treatments have stopped.

Many of the involved centers are academic, non-profit, and/or governmental entities with an interest in advancing evidence-based medicine and research. Contributions made by centers are essential to evaluating the promise of HBO2 in various conditions and may lead to adoption them as new UHMS indications. This review provides a snapshot to clinicians of diagnoses that have been treated by HBO2 that are not officially on the UHMS indications list. This can be useful in situations where patients are not improving with standard therapy and other approaches are being sought that could address hypoxia and inflammation. It also focuses attention on specific diagnoses worthy of further study.

Limitations and strengths of the present study

The registry has limitations. To keep the time required for data entry to a minimum only a specific set of outcomes are collected. The registry does not include extensive data on medications, other co-morbid conditions, or laboratory results. While this approach has been successful at making the registry practical for centers to adopt, it does affect the scope of conclusions that can be drawn.

The registry undergoes active review and expansion over time, so not all questionnaires currently in use existed in the registry when it started. Missing data, particularly for the EQ5D in earlier cases, is understandable as this questionnaire was added later in registry development. Also, data collection can be missed if patients stop treatment early or unexpectedly or transfer to another center. Nevertheless, the missing data are a limitation of the registry. The registry does not include a control or standard treatment group for every condition, so it is not possible to compare outcomes with no treatment or placebo. Registry results can be compared with publicly reported treatment success rates of those using standard therapy.

For the analyses, the data were reviewed to fix indications that were misclassified (i.e., UHMS-approved indications that were categorized as "Other" or "Other" indications that were inappropriately classified as a UHMS-approved indication). There may be cases, however, that were missed. The data are dependent on data-entry and there may be variation in data entry quality between centers. Work is ongoing with data quality checks throughout registry centers to ensure these problems are limited in the future.

Nevertheless, the strength of the registry is that it allows outcomes from less common conditions to be combined across centers, which provides information that no individual center would be able to achieve independently. The accumulated results identify areas where more detailed trials would be useful. Also, some centers are beginning long-term follow-up with treated patients to gather data on satisfaction with and longevity of the results. This will expand the capabilities of the registry although the responses will be affected by selection bias.

Conclusions

The registry is providing standardized outcome data on conditions that are not currently UHMS-approved but are being treated with HBO2 at participating centers. This is adding prospectively collected data to the mostly retrospective data that exists in the literature. Results show statistically significant improvements in patient reported outcomes, such as quality of life, for inflammatory bowel disease, frostbite, and PASC. HBO2 is also being used to improve surgical outcomes for pterygium and hypospadias procedures and to treat complications from facial filler injections. HBO2 is also being tried for difficult cases involving hypoxia such as femoral head necrosis, Raynaud's syndrome, and chronic anal fissures.

As time goes on and as more centers participate, significant trends can be identified, which may identify a valuable treatment option for medical conditions where hypoxia and inflammation are important contributing factors. Indications developed at a few centers initially can also be expanded to other centers based on the outcomes.

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Data availability

The data and code used for the study are available from the Steering Committee of the Multicenter Registry for Hyperbaric Oxygen Treatment upon reasonable request.

Conflicts of Interest

None declared.

Author Contributions

HT-Investigation, formal analysis, writing-original draft, writing-review and editing
JRR-Conceptualization, methodology, supervision, writing-review and editing
ZZ-Data curation, formal analysis
JAP-Conceptualization, investigation, statistical support
PMH-Investigation, methodology
EMS-Investigation, writing-review and editing
JLP-Methodology, supervision, formal analysis, writing-review and editing
JCB-Conceptualization, funding acquisition, formal analysis, supervision, writing-original draft, writing-review and editing

Abbreviations

ATA: Atmospheres absolute
COVID: Coronavirus disease
HBO2: Hyperbaric oxygen
IBD: Inflammatory bowel disease
NSI: Neurobehavioral symptom inventory
PASC: Post acute sequelae of COVID syndrome
QOL: Quality of life
RECORD: REporting of studies Conducted using Observational Routinely collected health Data
REDCap: Research Electronic Data Capture
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UHMS: Undersea and Hyperbaric Medical Society

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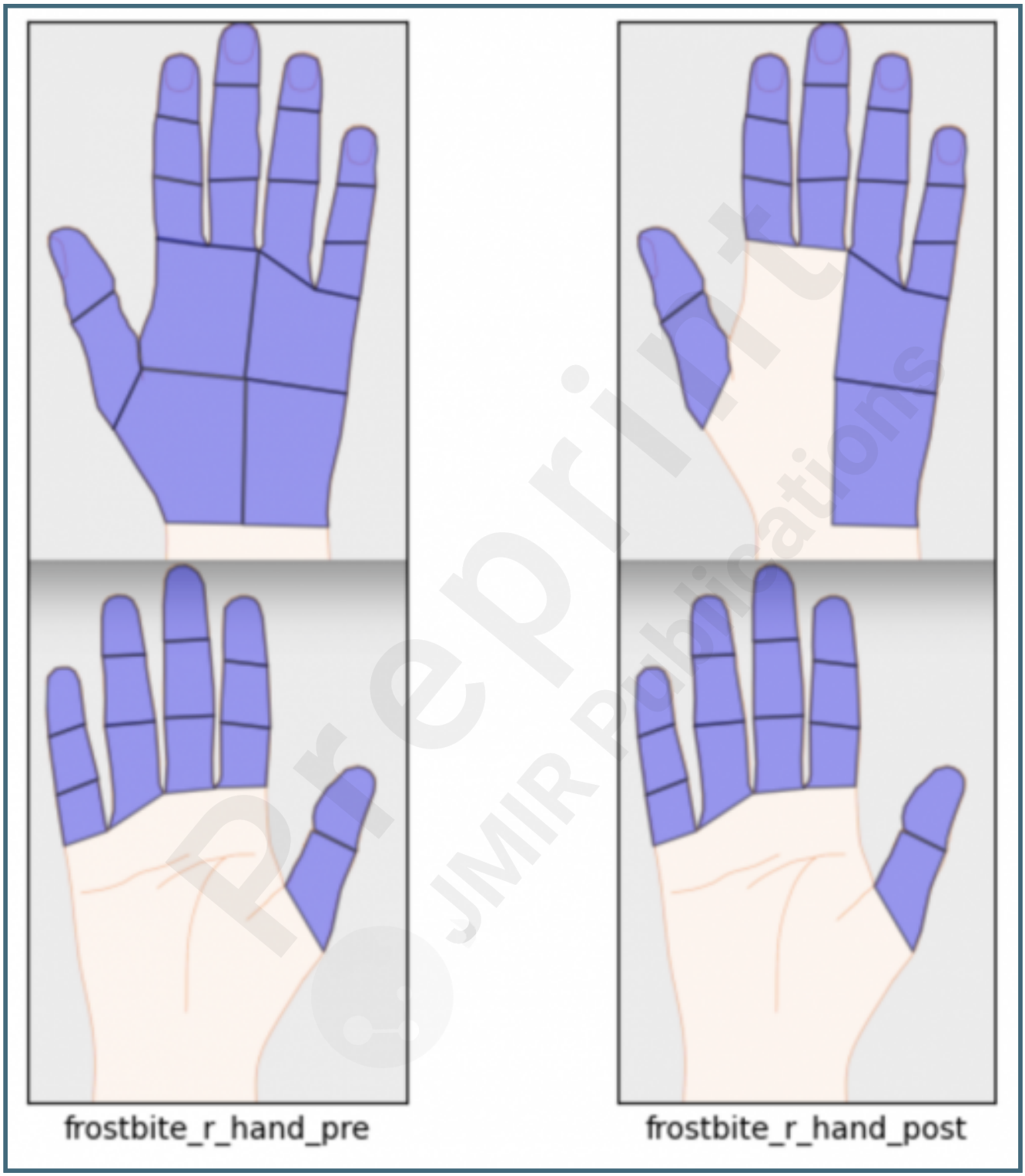
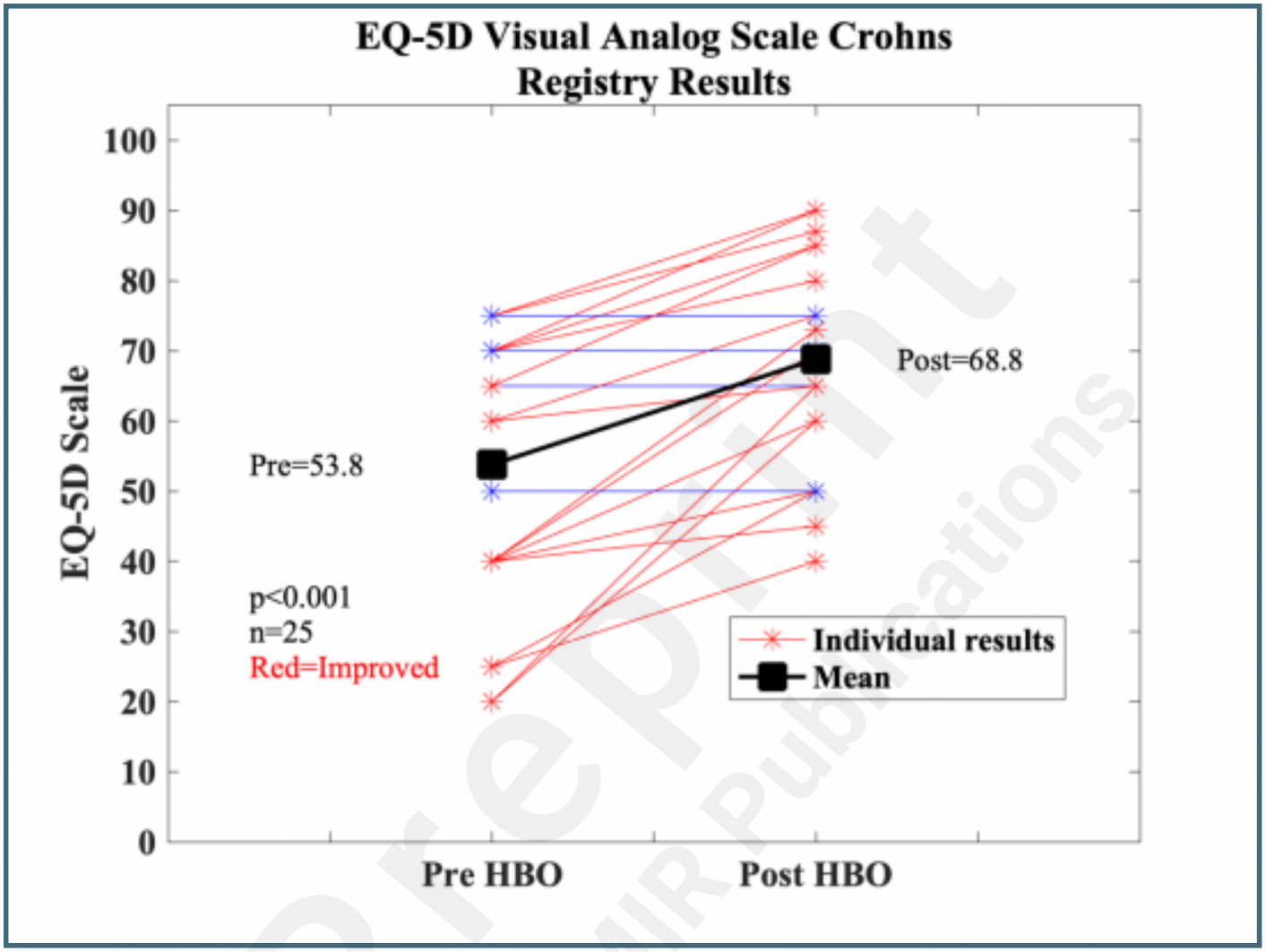
Supplementary Files

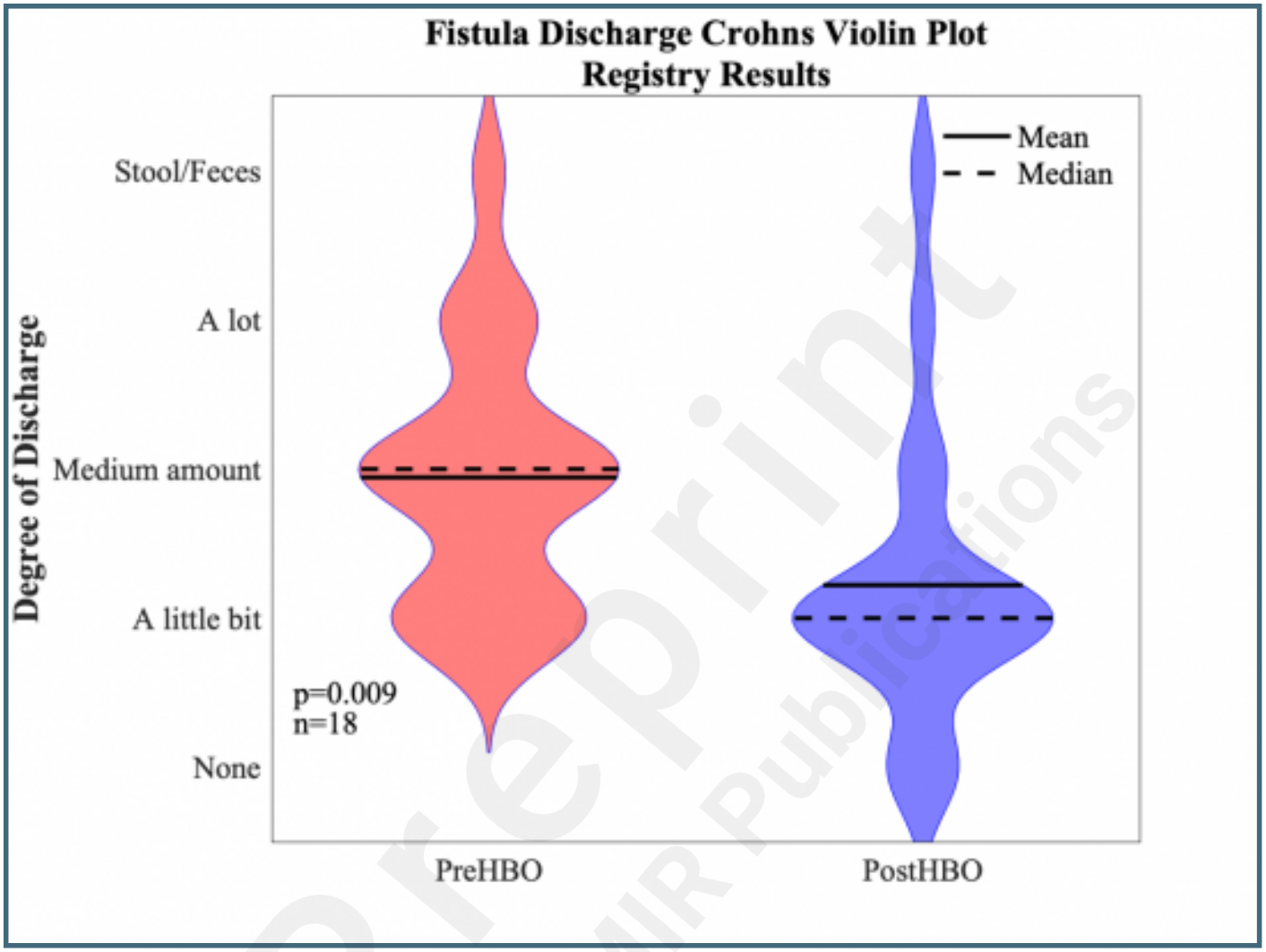
Figures

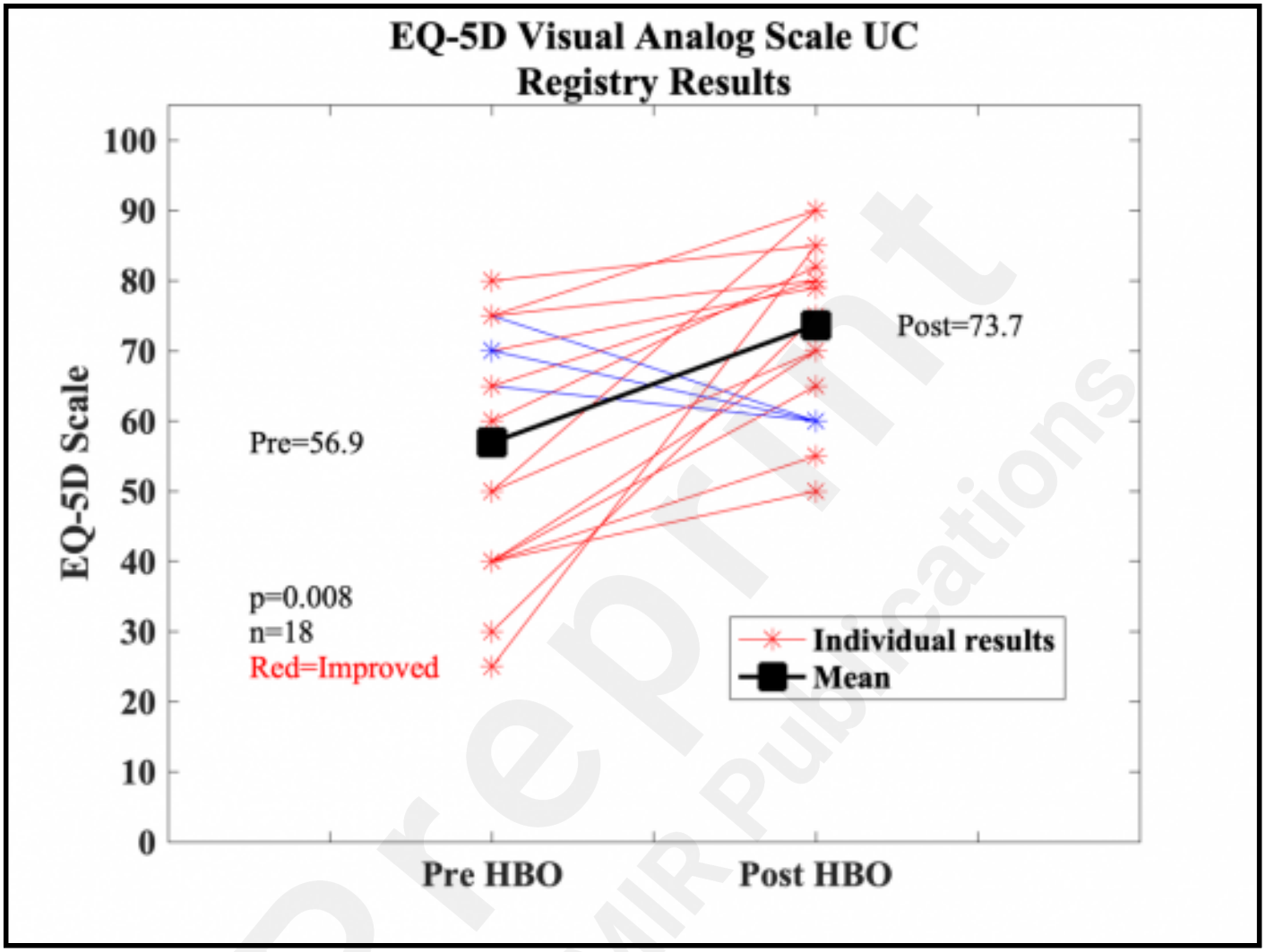
Data entry screen for frostbite injuries. The registry provides different approaches to data entry to make data entry easy and consistent.

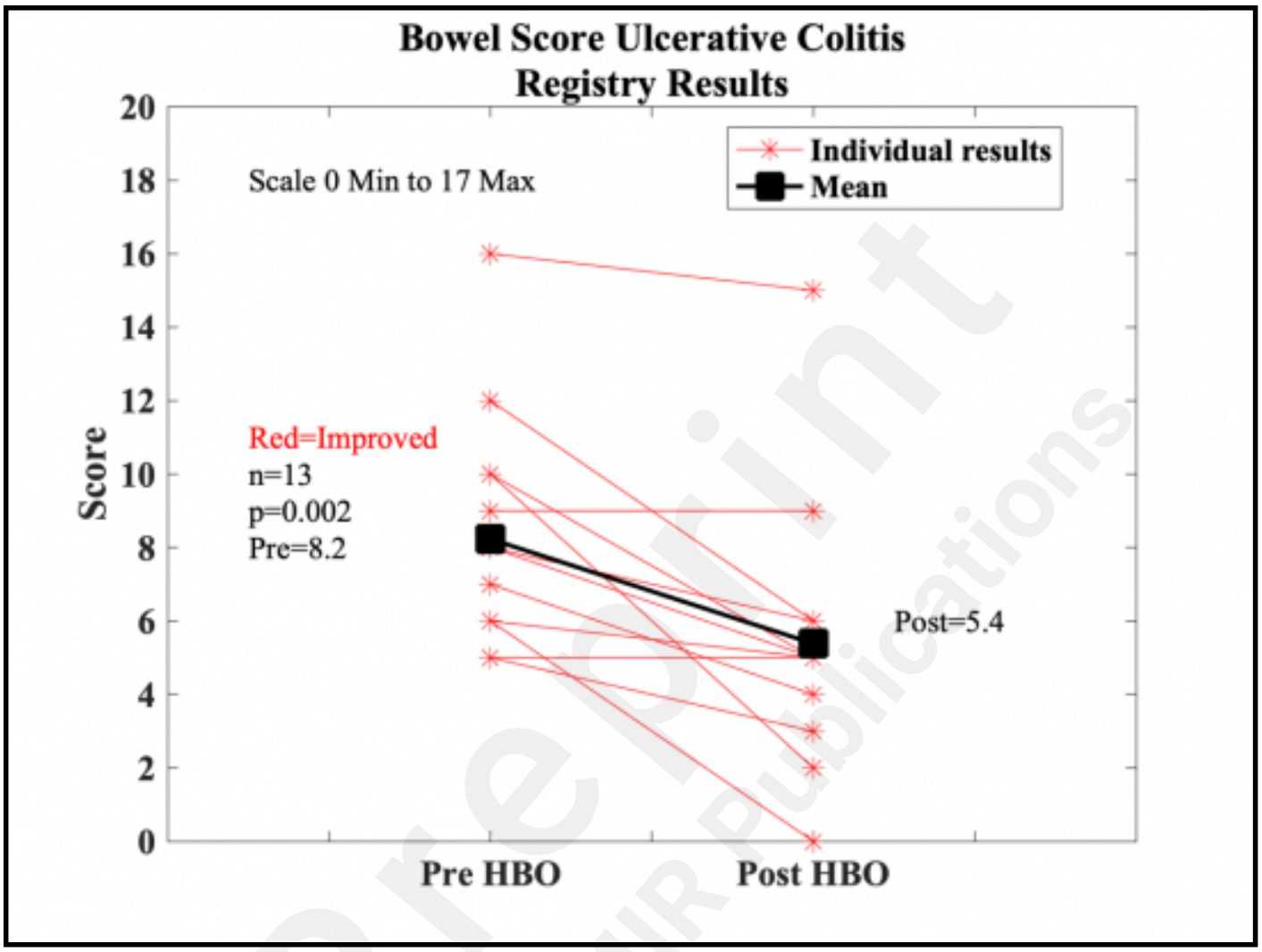


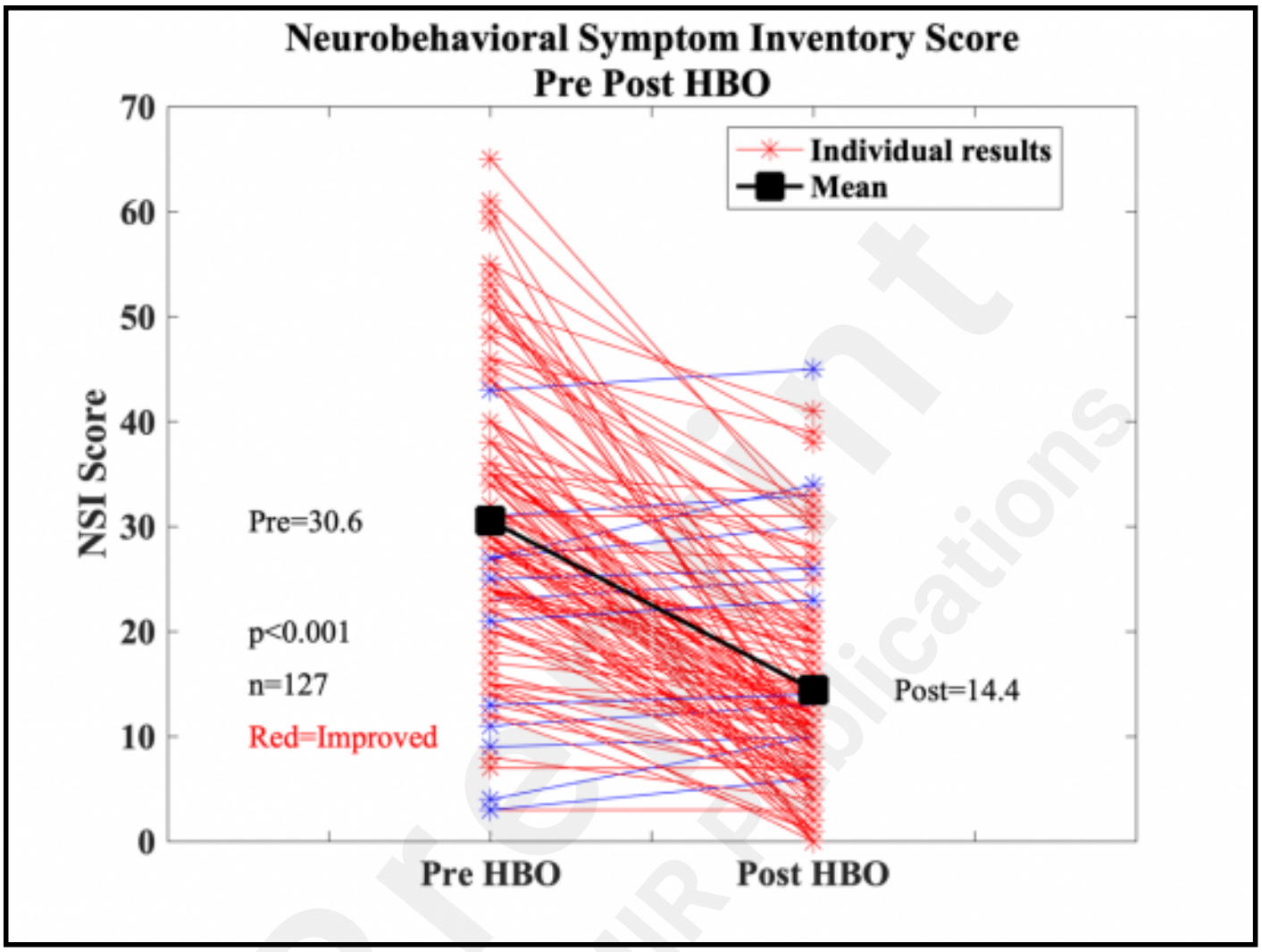
Results from the EQ-5D visual analog scale for patients with Crohn’s disease. 20 patients had complete pre and post HBO2 data. A sensitivity analysis using a best, worst, and average case for missing data shows the results are significant in all those cases.











Multimedia Appendixes

Perianal Crohn's Symptom Index.

URL: http://asset.jmir.pub/assets/8136876c924201b020ffd63a87b30676.pdf

Bowel Symptoms Questionnaire.

URL: http://asset.jmir.pub/assets/5fe9947a583bfd691b872b92a5fee3e5.pdf

CONSORT (or other) checklists

RECORD checklist.

URL: http://asset.jmir.pub/assets/f2dfcce57357c39ec9b551b195300d44.pdf