Hyperbaric oxygen therapy in patients with hemorrhagic radiation cystitis: A population-based, retrospective cohort study

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ABSTRACT

Introduction: Hyperbaric oxygen therapy (HBOT) can be used to manage hemorrhagic radiation cystitis, although small studies demonstrate variable effectiveness. This study aimed to evaluate the epidemiology, predictors, and clinical effectiveness of HBOT using a large population-based cohort.

Methods: A retrospective cohort study of pelvic cancer patients with post-radiotherapy (RT) hemorrhagic cystitis in Ontario, Canada (2002−2021). HBOT users and non-users were followed for at least one year post-treatment, March 2024, or death. We measured HBOT use, identified

predictors via logistic regression, and compared healthcare outcomes (emergency visits, hospitalizations, procedures, and blood transfusions) using multivariate difference-in-difference analysis at one- and three-year intervals.
Results: Among post-RT pelvic cancer patients with hemorrhagic cystitis, HBOT use was 1.4% (707/51 714). Older age, non-prostate/cervical malignancy, lower income, and greater distance to center were associated with less HBOT use. The rate of emergency visits (3.3, 95% confidence interval [CI] 3.2−3.4 vs. 1.8, 95% CI 1.7−1.9 visits per person; p<0.001), hospitalizations (0.9, 95% CI 0.9−1.0 vs. 0.6, 95% CI 0.5−0.6 visits per person; p<0.001), procedures (2.8, 95% CI 2.6−2.9 vs. 1.1, 95% CI 1.0−1.2 procedures per person; p<0.001), and blood transfusions (0.6, 95% CI 0.6−0.7 vs. 0.5, 95% CI 0.4−0.5 transfusions per person; p<0.001) all significantly decreased one year post-HBOT, with sustained effects at three years.
Conclusions: At one- and three-year followups, HBOT use was associated with significant reductions in emergency visits, hospitalizations, procedures, and transfusions among a large cohort with post-RT hemorrhagic cystitis. These findings support the consideration of HBOT as an effective therapeutic option in this population, though persistent access disparities highlight the need for targeted interventions and further study.

INTRODUCTION

The most common reason for radiotherapy (RT)- associated hospitalization in the United States is radiation cystitis.[1] Hemorrhagic symptoms are difficult to manage and impose significant morbidity and healthcare burden.[2–4] Approximately half of hospitalized patients require cystoscopy, while 25% need a blood transfusion.[2] With a median length of stay of 4 days, inpatient costs for a patient with hemorrhagic radiation cystitis range from $7000-9000 US dollars (USD).[2,5] As RT remains a mainstay of treatment for pelvic malignancies, with increasing adoption particularly for colorectal cancers,[6] management of the long-term adverse effects of radiation cystitis warrants attention.

Hyperbaric oxygen therapy (HBOT) is used to manage refractory hemorrhagic symptoms in a minority of patients with radiation cystitis.[2,4] Administered in a pressurized chamber at roughly twice ambient pressure, 100% oxygen reverses radiation-induced hypoxia and promotes neovascularization and fibroblast proliferation.[7] When defined by the absence/reduction of hematuria, small studies (<200 patients) suggest response rates ranging from 20-100%.[8–10] In a larger cohort (>1000 patients), Feldmeier et al. reported a 78% reduction in transfusions and 31% reduction in endoscopic procedures following HBOT.[11] The only randomized controlled trial (RCT) comparing HBOT with standard care found significant improvements in urinary quality of life at 6 months and 5 years, though early response predicted success.[12,13] Despite these encouraging findings, most studies remain limited by small sample sizes. In addition, current

literature has not examined factors influencing HBOT use, leaving gaps in our understanding of predictors and potential disparities.

Using a large, retrospective cohort of patients in Ontario, Canada, this study aimed to measure the epidemiology and predictors of HBOT use in patients with post-RT hemorrhagic cystitis. In addition, we sought to measure the impact of HBOT on emergency room visits, hospitalizations, procedural intervention and blood transfusions.

METHODS

Study design

We performed a population-based retrospective cohort study of post-RT pelvic cancer patients in Ontario, Canada (population= 16 million)[14] diagnosed with hemorrhagic cystitis from April 1st, 2002 to Mar 31st, 2021, stratified by HBOT users and non-users. Descriptive and inferential analyses were conducted to assess HBOT use and outcomes. Across a 19-year timeframe, we described the incidence, timing, and distribution of HBOT, and evaluated predictors using multivariate logistic regression. Four clinical outcomes- emergency visits, hospitalizations, procedures, and blood transfusions- were analyzed at one- and three-year intervals (i.e. three-years pre- and post-HBOT). A multivariate difference-in-difference (DiD) analysis compared outcomes between users and non-users at both time points.

Data sources

Data was derived from the Institute for Clinical Evaluative Sciences (ICES), an independent repository of heath services records in Ontario, Canada (http://www.ices.on.ca). ICES maintains administrative databases that capture the vast majority of publicly funded healthcare in the province, resulting in a highly representative source. Each database is coded at the record-level and is linkable across inpatient and outpatient encounters (Supp. Material 1).

Subjects

Individuals with a pelvic cancer diagnosis prior to March 31st, 2021 (prostate, colorectal, cervical, ovarian, uterine, female genital organs, male genital organs) were identified via the Ontario Cancer Registry (Figure 1, Supp. Material 2). Those with bladder cancer were not included given overlapping hematuria. Individuals who underwent at least one RT treatment from April 1st, 2002 to Mar 31st, 2021, following their cancer diagnosis date, were extracted. Next, individuals with hemorrhagic cystitis were identified from multiple databases following their first RT visit. The study index date was defined as the last date of RT or the date of the patient's first procedure for cystitis, whichever came first.

Patients were excluded for invalid death date, age (<18 or >106 years), non-Ontario resident (inconsistent access to public healthcare system), or invalid health record. The final cohort included 51,714 patients (Figure 1).

Exposure: HBOT

Patients with prior pelvic RT and hemorrhagic cystitis were followed until Mar 31st, 2023 to identify HBOT use (Figure 1). Users had ≥1 HBOT visit. We recorded the number of HBOT sessions, treatment duration, and completion of ≥40 sessions. HBOT facilities (n=12) were identified from the Ontario Hyperbaric Medicine Society (https://onhms.ca/page-18061), with additions from HBOT providers on the research team. Facilities were emailed to confirm when HBOT for hemorrhagic cystitis began, ensuring availability preceded the study period.

Covariates

Age, cancer type, Charlson co-morbidity score,[15] anticoagulant/antiplatelet use, neighborhood income and distance to nearest HBOT center were deemed clinically relevant co-variates influencing HBOT use and outcomes. Anticoagulant use and antiplatelet use were captured for patients aged ≥65 based on coverage through the provincial drug benefit plan (Supp. Material 2). Distance to HBOT facility for users was captured using postal code information from the patient's residence and the location of the facility where HBOT was received. For non-users, the facility with the shortest distance from the patient's place of residence was assigned.

Outcomes

Patients were followed until at least one-year post-HBOT treatment, March 31st, 2024 or death. Primary outcomes included emergency room visits, hospitalizations, procedures and blood transfusions. Emergency visits and hospitalizations, for any reason (not specific to hemorrhagic cystitis), were identified using the National Ambulatory Care Reporting System and Discharge Abstract Database (Supp. Material 2). Procedures included any of the following: cystoscopy, clot evacuation/irrigation, control of bleeding and transurethral resection of bladder tumor or transurethral resection of prostate, while transfusions were extracted from inpatient and outpatient records. Outcomes were evaluated at one- and three- year time intervals before and after HBOT. Seven percent of HBOT users (48/707) lacked the full three-year follow-up, thus were included only in the one-year analysis.

Statistical analysis

Descriptive analyses characterized HBOT incidence, timing, and facility distribution. Logistic regression identified predictors of HBOT use. Based on univariate analyses, absence of co-linearity and clinical relevance, the following variables were adjusted for in the multivariate model: age (continuous), cancer type (categorical), Charlson score (categorical), anticoagulant use (binary), antiplatelet use (binary), neighbourhood income (categorical) and distance from HBOT centre (categorical).

A multivariate DiD analysis was completed for each clinical outcome at both one- and three-year intervals. The exposed group consisted of HBOT users, as defined above, and the unexposed group consisted of non-users. For non-users, one date was set as the start of the "pre" period and another as the start of the "post" period. The pre-period date was chosen to match the

distribution of first HBOT dates in the exposed group. The post- period date was set to be the same number of days after the pre-period date as the length of HBOT treatment for the matched exposed individual. Non-users were matched to users in a 3:1 ratio on the basis of age (5-year categorical groups), cancer type, distance quintile and time from index enrollment to the date defining the pre-period (matched using quartiles from the exposed group). The following additional confounders were adjusted for in the final model based on statistical significance, clinical relevance and absence of co-linearity: Charlson score, neighbourhood income, anticoagulant/antiplatelet use. Statistical significance was set at $p<0.05$. All statistics were performed in SAS® Enterprise Guide 8.3.

Ethics

Ethics approval was obtained from Sunnybrook Health Sciences Centre Research Ethics Board (#6025). Patient consent was waived due to the administrative nature of the data.

RESULTS

Subject demographics

A total of 51, 714 patients were included in the final analysis: 51, 007 (98.6%) non-users and 707 (1.4%) HBOT users (Figure 1, Table 1). Overall, the average age was 71 years old (±10.5), and most patients were male (83.1%, 42, 978/51, 714). The most common type of cancer was prostate (70.3%, 36, 374/51, 714); however, cervical cancer patients had the highest relative proportion of HBOT use (3.6%, 70/1, 961). There were no significant differences in co-morbidities between HBOT users and non-users. Cumulatively, 37.1% of people aged 65 and older had documented use of either an oral anticoagulant, anti-platelet agent or both (14, 412/ 38, 839) (Supp. Material 3). The proportion of HBOT users was lower in rural settings than in urban settings.

Timing, distribution, and predictors of HBOT use

The median time from index date (last date of RT/ date of first procedure) to first HBOT visit was 771 days (IQR=270-2, 037). The median number of visits per person was 34 (IQR= 26-46), while the median time per visit was 120 minutes (IQR= 118-134). The median time from first to final treatment session was 57 days (IQR= 42-98). Only 37.5% of HBOT users completed at least 40 treatment sessions (265/707). A total of 123 providers delivered HBOT in the province, of which over 70% were anesthesiologists or general practitioners. HBOT users traveled a median distance of 16 km (IQR= 6-51) to reach their treatment center. In contrast, non-HBOT users lived a significantly greater distance from the nearest HBOT clinic, with a median of 24 km (IQR = 8-78; $p<0.001$) (Table 1, Figure 2).

Older patients were significantly less likely to undergo HBOT (aOR 0.96, 95%CI: 0.95-0.97; $p<0.001$) (Table 2). All cancer types had lower odds of HBOT use compared to prostate cancer, with the exception of cervical cancer (aOR 1.22, 95%CI: 0.91-1.65; $p=0.19$). Those with a Charlson score of two had greater odds of HBOT use compared to those with a score of zero

(aOR 1.25, 95%CI: 1.04-1.52; p=0.02). History of anticoagulant and/or antiplatelet use did not influence HBOT use. Patients who lived in the wealthiest neighbourhood income quintile had greater odds of undergoing treatment compared to those in the lowest income quintile (aOR 1.57, 95%CI: 1.21-2.04; p<0.001). Finally, individuals furthest from an HBOT center (44–89 km and 89–1, 211 km) had significantly lower odds of receiving HBOT compared to those in the nearest quintile (aOR 0.51, 95%CI: 0.39-0.66 and aOR 0.56, 95%CI: 0.43-0.73; p<0.001).

Frequency of clinical outcomes post-HBOT

The number of emergency visits, hospitalizations, procedures and blood transfusions decreased significantly at both one and three-year intervals following HBOT (Table 3). At one-year, the rate of emergency visits (3.3, 95%CI: 3.2-3.4 vs. 1.8, 95%CI: 1.7-1.9 visits per person; p<0.001), hospitalizations (0.9, 95%CI: 0.9-1.0 vs. 0.6, 95%CI: 0.5-0.6 visits per person; p<0.001), procedures (2.8, 95%CI: 2.6-2.9 vs. 1.1, 95%CI: 1.0-1.2 procedures per person; p<0.001), and blood transfusions (0.6, 95%CI: 0.6-0.7 vs. 0.5, 95%CI: 0.4-0.5 transfusions per person; p<0.001) all significantly decreased. Outcomes remained significantly less at three-year intervals as well (Table 3).

Comparison of clinical outcomes between HBOT users and non-users

Parallel trends were assumed given baseline similarities and the expectation that, absent treatment, outcome differences would remain stable over time. Among post-RT patients with hemorrhagic cystitis, there was a significant reduction in emergency visits between HBOT users and non-users at both one-year (adjusted DiD (aDiD) estimate= -1.22) and three-year intervals (aDID estimate= -0.75; p<0.001) (Table 4). Hospitalizations were significantly reduced among HBOT users compared to non-users at both one year (aDiD estimate = -0.28, p<0.001) and three years post-treatment (aDiD estimate = -0.21, p=0.004). The number of procedures between HBOT users and non-users were reduced significantly by 1.35 and 1.32 procedures per person at one and three years, respectively (p<0.001). Finally, transfusions were reduced between HBOT users and non-users at one-year (aDID estimate= -0.10, p=0.01) but not three years (aDID estimate= 0.03, p=0.77).

DISCUSSION

This cohort represents one of the largest reported groups of patients with post-RT hemorrhagic cystitis treated with HBOT. Overall use was low (1.4%), with most users having a history of prostate cancer. Older age, non-prostate or cervical malignancy, lower income, and greater distance from HBOT centers were associated with less use. HBOT was associated with significant reductions in emergency visits, hospitalizations, procedures, and blood transfusions at one- and three-year follow-up.

When comparing studies evaluating HBOT for hemorrhagic radiation cystitis, it is important to consider the varying definitions of treatment success, often categorized into three domains: reduction in hematuria, improvement in lower urinary tract symptoms (LUTS), and

decreased healthcare utilization. Several systematic reviews and meta-analyses present data from small cohort studies through 2024, reporting overall response rates ranging from 20-100% among treated patients.[8–10] In most studies though, treatment success was defined primarily by the absence or reduction of hematuria, offering a narrow definition of therapeutic benefit. RICH-ART, the only RCT comparing HBOT with standard care (another compared HBOT with hyaluronic acid)[16], found meaningful improvements in urinary quality of life at 6 months and 5 years.[12,13] While the extended follow-up is valuable, outcomes omitted hematuria (often the most burdensome symptom) and its relationship to downstream service needs. Moses et al. reported short-term improvement in multiple patient-reported symptoms (including hematuria) among 470 HBOT patients; however, the study also did not fully address translation to healthcare delivery.[17] Reliance on hematuria or LUTS as outcomes may overlook the multidimensional burden of radiation cystitis and broader utilization benefits. Feldmeier et al.'s US-based cohort remains the only other study assessing utilization metrics, showing comparable findings to ours, including a 78% reduction in blood transfusions and 31% reduction in endoscopic procedures, though with shorter follow up.[11]

Radiation cystitis imposes a substantial burden on both patients and the healthcare system. In the three years prior to HBOT, our cohort experienced a high rate of healthcare utilization, with an average of 5.6 emergency visits, 1.4 hospitalizations, 4.2 procedures and 0.9 blood transfusions per person. Reflecting this clinical burden, a parallel analysis by Rapariz-González et al. found that 56% of patients reported a fair to major impact of their radiation cystitis-associated urinary symptoms on daily functioning and well-being.[18] These findings represent not only significant morbidity, but also a considerable economic burden. Based on a median length of stay of 4 days, prior US analysis reported a median hospitalization cost of $7, 151 USD per admission for radiation cystitis.[5] While HBOT involves considerable time and financial commitment- averaging 68 hours per patient- it may provide long-term value, with Medicare data showing a 37% reduction in spending among those who completed ≥40 sessions.[11] Finally, patients in our cohort residing in low-income neighborhoods and located further from an HBOT facility were significantly less likely to use HBOT, underscoring potential geographic and socioeconomic barriers to care consistent with broader access literature.[19,20] Together, these findings highlight the need for health systems strategies that promote equitable access to effective therapies like HBOT.

While this represents one of the largest HBOT cohorts to date, several limitations apply. Use of administrative data introduces potential misclassification, as radiation-induced cystitis cannot be directly identified given the absence of specific diagnosis codes, and HBOT may not always have been used for cystitis. Nevertheless, hemorrhagic cystitis was documented following RT, and HBOT was initiated after the first episode of hemorrhagic cystitis, supporting a temporal relationship. We were also unable to assess individualized RT dose/ spatial distribution or symptom severity, which limited our ability to explore potential dose-response relationships or whether symptom burden influenced HBOT effectiveness. Spontaneous

improvement in hemorrhagic cystitis and the absence of severity-based matching introduce potential residual confounding in the observed treatment effects. Finally, inclusion of single-course radiotherapy patients could be inferred to represent a palliative subgroup, though the cohort's age distribution and number of HBOT sessions suggests these patients were not meaningfully represented in the overall sample.

CONCLUSIONS

In this large cohort, HBOT was associated with significant reductions in emergency visits, hospitalizations, procedures and blood transfusions among patients with post-RT hemorrhagic cystitis. However, patients from a low-income neighbourhood and those residing further from an HBOT center were less likely to use HBOT. Considering these treatment benefits, future work should explore HBOT access constraints with a view towards minimizing barriers to care.

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Conflicts of interest: Jordan Tarshis and Fahad Alam are shareholders of Restore Hyperbarics Inc., one of the hyperbaric centres included in this analysis.

Data availability statement: *The data sets generated during and analyzed during the current study are not publicly available as they were sourced from ICES institutional database. Data are however available from the authors upon reasonable request and with permission of ICES.*

FIGURES AND TABLES

Figure 1. Selection of study sample. Drawn from population of Ontario, Canada (approx. 16 million people). *Pelvic cancer= prostate, colorectal, cervical, uterine, ovarian, female genital organs (vaginal, vulvar, unspecified), male genital organs (penis, testis, unspecified). RT: radiotherapy.

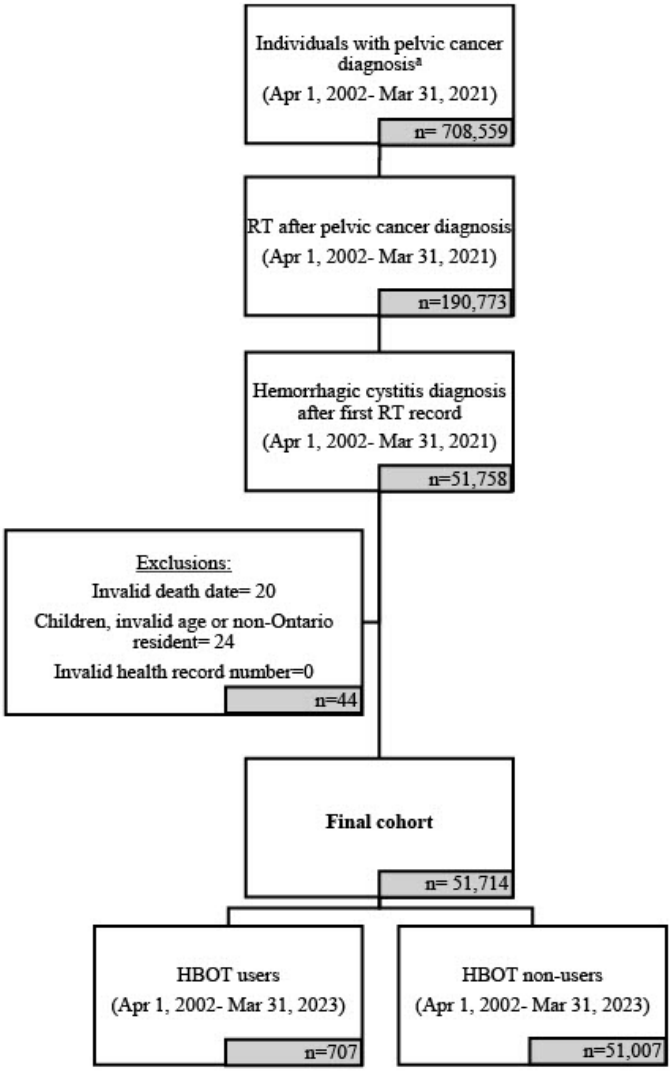

Figure 2. Distribution of individuals with post-radiation hemorrhagic cystitis and hyperbaric oxygen therapy (HBOT) centers (red) across Local Health Integration Network divisions in Ontario, Canada between April 1, 2002, and March 31, 2021.

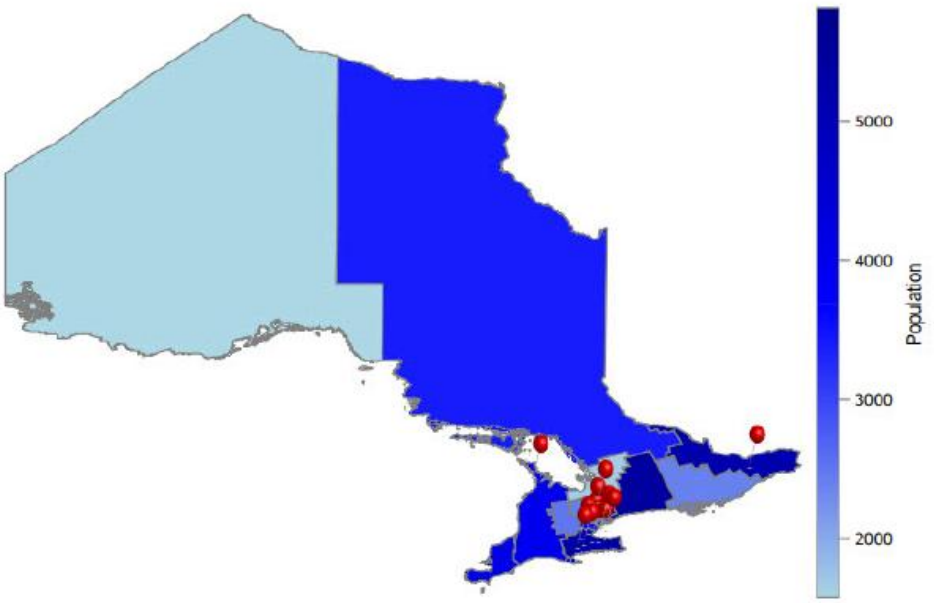

Table 1. Demographics and clinical features of study sample					
Variable	**Value**	**No HBOT use**	**HBOT use**	**Total**	**p (±)**
		n=51 007	**n=707**	**N=51 714**	
Age	Mean ± SD	70.69±10.48	66.26 ± 10.87	70.63±10.50	<0.001
	Median (IQR)	72 (65-78)	67 (60-74)	72 (65−78)	<0.001
Sex	Male	42 400 (83.1%)	578 (81.8%)	42 978 (83.1%)	0.334
	Female	8607 (16.9%)	129 (18.2%)	8736 (16.9%)	
Cancer type	Prostate	35 835 (70.3%)	539 (76.2%)	36 374 (70.3%)	<0.001
	Colorectal	8701 (17.1%)	52 (7.4%)	8753 (16.9%)	
	Uterine	2884 (5.7%)	23 (3.3%)	2907 (5.6%)	
	Cervical	1891 (3.7%)	70 (9.9%)	1961 (3.8%)	
	Female genital organs**	589 (1.2%)	11 (1.6%)	600 (1.2%)	
	Ovarian	526−530*	≤5	531 (1.0%)	
	Male genital organs***	581 (1.1%)	7 (1.0%)	588 (1.1%)	
Comorbidities	Atrial fibrillation	5056 (9.9%)	56 (7.9%)	5112 (9.9%)	0.078
	Ischemic stroke	2552 (5.0%)	29 (4.1%)	2581 (5.0%)	0.274

	Deep vein thrombosis	1208 (2.4%)	16 (2.3%)	1224 (2.4%)	0.855
	Pulmonary embolism	676−680*	≤5	681 (1.3%)	0.152
	Immune thrombocytopenia	32−36*	≤5	37 (0.1%)	0.484
	Cerebral venous thrombosis	≤5	0 (0.0%)	≤5	0.792
Neighbourhood income	1- lowest	9085 (17.8%)	97 (13.7%)	9182 (17.8%)	0.001
	2	10 295 (20.2%)	136 (19.2%)	10 431 (20.2%)	
	3	10 029 (19.7%)	140 (19.8%)	10 169 (19.7%)	
	4	10 209 (20.0%)	132 (18.7%)	10 341 (20.0%)	
	5- highest	11 248 (22.1%)	200 (28.3%)	11 448 (22.1%)	
	Missing	141 (0.3%)	2 (0.3%)	143 (0.3%)	
Rurality	Urban	43 810 (85.9%)	639 (90.4%)	44 449 (86.0%)	0.002
	Rural	7155 (14.0%)	67 (9.5%)	7222 (14.0%)	
	Missing	42 (0.1%)	1 (0.1%)	43 (0.1%)	
Distance from HBOT center (km)	Mean ± SD	68.99±132.73	47.15±82.44	68.69±132.19	<0.001
	Median (IQR)	24 (8−78)	16 (6−51)	24 (8−77)	<0.001

Note: ±Bivariate analyses were conducted using one-way ANOVA for parametric data and Chi-squared or Kruskal-Wallis tests for non-parametric data, as appropriate. *Range given limitations in coding. **Female genital organs=vaginal, vulvar, unspecified. ***Male genital organs=penis, testis, unspecified. HBOT: hyperbaric oxygen therapy.

Table 2. Logistic regression evaluating population−level predictors of HBOT use

Variable	**Value**	**Univariable analysis**		**Multivariable analysis**	
		OR (95% CI)	**p**	**aOR (95% CI)**	**p**
Age		0.965 (0.959−0.971)	<0.001	0.961 (0.953−0.969)	<0.001
Cancer type	Cervical vs. prostate	2.461 (1.911−3.171)	<0.001	1.222 (0.906−1.648)	0.190
	Female colorectal* vs. prostate	0.49 (0.313−0.766)	0.002	0.373 (0.236−0.589)	<0.001
	Male colorectal* vs. prostate	0.355 (0.249−0.508)	<0.001	0.296 (0.205−0.426)	<0.001
	Female genital, ovarian and uterine vs. prostate	0.648 (0.468−0.899)	0.009	0.515 (0.369−0.719)	<0.001
	Male genital vs. prostate	0.801 (0.378−1.696)	0.562	0.44 (0.205−0.946)	0.036
Charlson score	1 vs. 0	0.882 (0.579−1.344)	0.558	1.076 (0.703−1.645)	0.737

	2 vs. 0	1.262 (1.049−1.518)	0.014	1.254 (1.037−1.516)	0.019
	3+ vs. 0	0.702 (0.537−0.917)	0.010	0.804 (0.61−1.058)	0.120
Anticoagulant use	Yes vs. no	0.753 (0.586−0.966)	0.026	1.08 (0.832−1.403)	0.562
Antiplatelet use	Yes vs. no	0.701 (0.555−0.886)	0.003	1.001 (0.782−1.283)	0.992
Neighbourhood income**	2 vs. 1 − lowest	1.193 (0.904−1.573)	0.212	1.191 (0.902−1.574)	0.217
	3 vs. 1	1.234 (0.937−1.625)	0.134	1.238 (0.938−1.634)	0.132
	4 vs. 1	1.21 (0.919−1.593)	0.175	1.203 (0.91−1.591)	0.194
	5 vs. 1 − highest	1.616 (1.251−2.087)	<0.001	1.571 (1.213−2.036)	<0.001
	6 vs. 1	0.813 (0.591−1.12)	0.205	1.075 (0.765−1.511)	0.676
Distance from HBOT center***	2 vs. 1 − nearest	0.841 (0.676−1.046)	0.121	0.812 (0.652−1.012)	0.064
	3 vs. 1	1.011 (0.821−1.246)	0.916	0.911 (0.736−1.127)	0.390
	4 vs. 1	0.515 (0.4−0.663)	<0.001	0.509 (0.392−0.66)	<0.001
	5 vs. 1 − furthest	0.566 (0.443−0.722)	<0.001	0.562 (0.432−0.73)	<0.001

Multivariable logistic regression analysis included the following variables: age, cancer type, Charlson score, anticoagulant use, antiplatelet use, neighbourhood income and distance from HBOT center. *Colorectal cancer was stratified by sex during regression due to significant overlap between sex and cancer type as confounders. **The sixth neighbourhood income quintile represents "rural." ***Distance quintiles were as follows: 0−6.2 km, 6.2−13.7 km, 13.7−44.3 km, 44.3−88.7 km, 88.7−1211 km. aOR: adjusted odds ratio; CI: confidence interval; HBOT: hyperbaric oxygen therapy; OR: odds ratio,

Table 3. Rate of clinical outcomes pre- and post- HBOT			
One year			
Outcome	**Pre-HBOT (per person, 95%CI)**	**Post-HBOT (per person, 95% CI)**	**p (±)**
Emergency room visits	3.29 (3.16−3.43)	1.76 (1.66−1.86)	<0.001
Hospitalizations	0.95 (0.88−1.02)	0.58 (0.53−0.64)	<0.001
Procedures	2.76 (2.64−2.89)	1.12 (1.05−1.20)	<0.001
Blood transfusions	0.61 (0.56−0.67)	0.46 (0.41−0.51)	<0.001
Three years			
Emergency room visits	5.57 (5.4−5.75)	4.05 (3.90−4.20)	<0.001
Hospitalizations	1.40 (1.32−1.49)	0.91 (0.85−0.99)	<0.001
Procedures	4.18 (4.03−4.34)	2.31 (2.20−2.43)	<0.001
Blood transfusions	0.95 (0.88−1.03)	0.78 (0.72−0.85)	<0.001

±Bivariate testing was conducted using non-parametric chi-squared testing. CI: confidence interval; HBOT: hyperbaric oxygen therapy.

Table 4. Matched difference-in-difference comparison of clinical outcomes among HBOT users vs. non-users									
		One-year interval				**Three-year interval**			
Outcome	**Analysis**	**Unadjusted model**		**Adjusted model**		**Unadjusted model**		**Adjusted model**	
		Estimate	**p**	**Estimate**	**p**	**Estimate**	**p**	**Estimate**	**p**
Emergency visits	Post vs. pre	-0.323	<0.001	-0.325	<0.001	-0.765	<0.001	-0.776	<0.001
	Exposed vs. unexposed	2.342	<0.001	2.368	<0.001	3.060	<0.001	3.113	<0.001
	DiD	-1.212	<0.001	-1.216	<0.001	-0.757	<0.001	-0.751	<0.001
Hospitali-zations	Post vs. pre	-0.087	<0.001	-0.087	<0.001	-0.284	<0.001	-0.285	<0.001
	Exposed vs. unexposed	0.699	<0.001	0.707	<0.001	0.826	<0.001	0.841	<0.001
	DiD	-0.281	<0.001	-0.283	<0.001	-0.205	0.004	-0.206	0.004
Procedures*	Post vs. pre	-0.286	<0.001	-0.287	<0.001	-0.544	<0.001	-0.547	<0.001
	Exposed vs. unexposed	2.149	<0.001	2.144	<0.001	2.806	<0.001	2.791	<0.001
	DiD	-1.353	<0.001	-1.354	<0.001	-1.322	<0.001	-1.323	<0.001
	Post vs. pre	-0.049	0.015	-0.049	0.014	-0.197	<0.001	-0.199	<0.001

Blood transfusions	Exposed vs. unexposed	0.490	<0.001	0.493	<0.001	0.590	<0.001	0.596	<0.001
	DiD	-0.102	0.011	-0.101	0.012	0.026	0.780	0.027	0.771

HBOT non-users vs. users matched 3:1 on age, cancer type, distance quintile, pre-exposure period. Model additionally adjusted for Charlson score, neighbourhood income, anticoagulant/antiplatelet use. *Procedures=cystoscopy, clot evacuation/irrigation, control of bleeding/transurethral resection of bladder tumor, transurethral resection of prostate. DiD: difference-in-difference; HBOT: hyperbaric oxygen therapy.