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Hyperbaric oxygen therapy in the treatment of late-onset hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation

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Introduction: Hemorrhagic cystitis (HC) is a common complication after allogeneic hematopoietic stem cell transplantation (HSCT), characterized by inflammation and bleeding of the bladder. Hyperbaric oxygen therapy (HBOT) has been shown to be effective in the treatment of radiation-induced HC. However, the optimal treatment for HC after allogeneic HSCT has not yet been established. Furthermore, limited research has been conducted on the use of HBOT in this setting. This study aimed to evaluate the effectiveness and safety of HBOT in patients with late-onset HC after allogeneic HSCT. Methods: Twenty-five-year (1998–2022) retrospective analysis performed in all consecutive patients with confirmed late-onset HC after allogeneic HSCT treated with HBOT at two centers in Portugal. Medical records were reviewed for clinical and laboratory features, primary indications for allogeneic HSCT, conditioning regimen, and treatment strategies for HC. Patients received 100% oxygen at 2.1–2.5 atmosphere absolute pressure (ATA) for 70–90-minute periods, once daily, five times per week. Complete clinical response was defined as the absence of macroscopic hematuria sustained for at least 2 weeks, and partial response was described as a downgrading in the severity of HC. Statistical significance was considered for values of $p < 0.05$. Results: The sample included 61 patients with a mean age of 28.0 (SD 14.2) years, 33 males. Complete response was achieved in 72.1% (n = 44) of patients and partial response in 14.8% (n = 9). Concerning patients with a complete response, the median number of HBOT sessions was 15.5 sessions (IQR 10.0-26.8). Patients treated with 10 or more sessions of HBOT had a higher rate of complete or partial response (OR 12.5, 95%CI 1.9–83.2, p-value < 0.05). There was no response in 8 (13.1%) patients, and 6 interrupted the treatments early. Only 2 patients suspended the HBOT due to a lack of clinical benefit. Conclusion: Our study supports using of HBOT as an adjunctive treatment for late-onset HC after allogeneic HSCT. Furthermore, 10 or more HBOT sessions delivered seem to impact the rate of HC resolution. Prospective, randomized, and well-controlled trials are needed to establish HBOT's definitive efficacy and safety.

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for many malignant and non-malignant hematologic conditions. Hemorrhagic cystitis (HC) is a syndrome characterized by hematuria and symptoms of urinary tract irritability[1]. It is an important cause of morbidity in patients undergoing allogeneic HSCT, leading to prolonged hospitalization, reduced quality of life, and increased healthcare costs[2,3]. However, the increase in post-allogeneic HSCT morbidity and mortality associated with hemorrhagic cystitis is controversial, highlighting the complex nature of this condition. The variability in data can be attributed to multiple factors, including disparities in patient selection, underlying clinical conditions, and several treatment protocols that can influence outcomes. Moreover, accurate mortality assessment is further complicated by the interaction of different risk factors, such as graft source, graft-versus-host disease (GvHD), and the development of opportunistic infections. These factors vary significantly among patient cohorts, making it challenging to establish a direct causal relationship between HC and increased morbidity and mortality[3].

The classification of HC is based on its onset after HSCT and is divided into early-onset and late-onset HC, reflecting different physiopathology. Early-onset HC occurs within the first week after HSCT, typically within 48 h after conditioning[3]. It results from the direct toxicity of the conditioning regimen on the urothelial mucosa, particularly from alkylating agents (cyclophosphamide, ifosfamide, busulfan) and total body irradiation. It is aggravated by concurrent thrombocytopenia and coagulation abnormalities[3,4].

Late-onset HC can be observed up to the first 6 months after HSCT, typically occurring during the neutrophil engraftment period[3]. It is associated with viral reactivation, particularly human BK and JC polyomaviruses, or adenoviruses, mainly type I and II[1–3]. Some studies also suggest the possible involvement of other viruses, such as cytomegalovirus (CMV), *Epstein-Barr* virus (EBV), human herpesvirus 6, and simian virus 40[1,5].

The pathogenesis of late-onset HC has yet to be understood entirely. However, it is believed that the conditioning regimen may lead to thinning the urothelial mucosal cell layer, which promotes viral reactivation and replication, particularly in immunosuppression. After immune reconstitution through engraftment, the infiltration of donor immune cells can cause tissue damage, ultimately resulting in the development of HC[3,4].

The risk factors can be divided into three groups, namely: (1) Patient-related factors – advanced age and cytopenias; (2) Transplant-related factors – unrelated donor, stem cells from umbilical cord blood or peripheral blood, myeloablative conditioning regimen and grade II-IV acute GvHD; (3) Virus-related factors – viral load in urine and plasma, with studies primarily focusing on BK polyomavirus[3,4].

In the majority of patients, HC often resolves with a conservative treatment. However, more aggressive interventions may be necessary in cases of life-threatening bleeding. The initial approach includes intravenous hydration, continuous bladder irrigation, transfusion support, addressing correctable factors (such as coagulopathies or infection), and pain management[1,5]. According to *Lunde et al.*. (2015), in a retrospective study of a large cohort ($n=1321$, 2003–2012) of HC after allogeneic HSCT patients, 89% of those receiving intravenous fluids experienced resolution of HC, compared to 75% receiving no therapy and 26% of those undergoing bladder irrigation[5].

The use of antiviral agents, as well as intravesical administration of anti-inflammatory or hemostatic agents, remains controversial. *Cesaro et al.* (2018) highlighted the efficacy of antiviral treatments, particularly cidofovir, in managing BK virus-associated HC. Based on uncontrolled studies, their review noted a complete clinical response in 74% of the patients treated with intravenous cidofovir. Although antiviral treatment with intravenous cidofovir is controversial due to the absence of randomized controlled studies, it may still be an option despite the uncertainty regarding its efficacy, optimal dose schedule, and the need to balance benefit against its renal side effects. Urologic fibrin glue applications have been successful in a limited number of uncontrolled studies. Several other treatments, such as administration of intravesical cidofovir, intravesical sodium hyaluronate, intravenous estrogens, intravenous immunoglobulins, leflunomide, mesenchymal cells, and cellular immune therapy, have only been used sporadically in a very limited number of patients or are still experimental[3]. Therefore, the optimal treatment for HC has not yet been established. Exploring new therapeutic strategies that are more effective and less toxic is essential.

Hyperbaric oxygen therapy (HBOT) is a promising complementary treatment option that improves the healing process of damaged urothelial tissue[5]. It has been recognized as a therapeutic option in the *ECIL guidelines for the prevention, diagnosis and treatment of BK polyomavirus-associated haemorrhagic cystitis in haemotopoietic stem cell transplant recipients* (recommendation level CIII)[3].

Studies with small sample sizes and case series have been published on HC after allogeneic HSCT and HBOT. The present study aims to evaluate the effectiveness and safety of HBOT in a cohort of patients with late-onset HC after allogeneic HSCT refractory to conservative treatments conducted at the two largest hyperbaric medicine centers in Portugal.

The primary outcome of this study is to evaluate the response rate to HBOT in patients who developed late-onset HC following allogeneic HSCT. The secondary outcomes are to assess potential predictive factors for treatment response and the safety profile of HBOT.

Materials and methods

This is a retrospective, observational, and multicentric study of patients who received HBOT for late-onset HC after allogeneic HSCT between January 1998 and December 2022 (25-years) at *Centro de Medicina Subaquática e Hiperbárica* (Hospital das Forças Armadas, Lisbon, Portugal) and *Unidade de Medicina Hiperbárica* (Unidade Local de Saúde de Matosinhos, E.P.E., Porto, Portugal).

The inclusion criteria for this study implied diagnosis of HC, defined by sustained hematuria along with symptoms of lower urinary tract irritability (dysuria, frequency, urgency) refractory to other treatments. Only cases of late-onset HC were considered, specifically those with a time interval between HSCT and the first day of macroscopic hematuria ranging from 1 week to 6 months. The exclusion criteria include gynecological bleeding, renal lithiasis, bleeding diathesis, or bacterial/fungal urinary tract infection[1].

The severity of HC was assessed prior to the initiation of HBOT, following the guidelines provided by *The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events*, *version 5.0* (CTCAE v5.0, 2017)[6]. The grading system is the following: grade 1 – asymptomatic microscopic hematuria; grade 2 – symptomatic macroscopic hematuria requiring urinary catheter placement or bladder irrigation and limiting instrumental activities of daily living (ADL); grade 3 – macroscopic hematuria requiring transfusions, intravenous medication, hospitalization, and/or elective endoscopic, radiological, or surgical interventions; grade 4 – macroscopic hematuria with life-threatening consequences requiring urgent radiological or surgical intervention; grade 5 – death.

The presence of viral agents in urine samples, including BK polyomavirus, adenovirus and CMV, was assessed using qualitative and/or quantitative polymerase chain reaction (PCR) techniques.

The HBOT was conducted in multi-place cylindrical walk-in chambers with 12 or 16-seat capacity, using the *HAUX-STARMED® system* (*Haux Life Support*, Karlsbad-Ittersbach, Germany). These chambers were equipped with audio and video entertainment systems and a heating/cooling system. The patients were stable hemodynamically, allowing them to be confined to the hyperbaric chamber under a certified nurse's supervision without a physician's direct presence. The treatment sessions involved a compression period during which the pressure inside the chamber was gradually increased from 1-atmosphere absolute pressure (ATA) to 2.1–2.5 ATA at a rate of 0.5-1 ATA per minute. This was followed by a period of 70–90 min at a pressure of 2.1–2.5 ATA, during which patients breathed oxygen. Depending on the specific center, the decompression profile followed either the *US Navy* or *Canadian Forces* decompression tables. Oxygen was administered to the patients through a nose/mouth mask or helmet, with a fraction of inspired oxygen (FiO_2) of 100%. The sessions were conducted daily, five days a week (Monday to Friday). Prior to starting HBOT, the patients were familiarized with the hyperbaric chamber, the interface, the compression/decompression procedure, and the safety protocols. All patients underwent a hyperbaric medicine specialist evaluation, including a *Eustachian* tube function assessment. No contraindications were observed in any of the patients.

The data were collected retrospectively by reviewing clinical records and medical files. The collected information included: (1) demographic variables - sex, age at initiation of HBOT; (2) transplant-related variables - primary indication for HSCT, conditioning regimen, source of allogeneic HSCT, acute GvHD grading according to *International Bone Marrow Transplant Registry Severity Index*; (3) HC-related variables - time interval from HSCT to the onset macroscopic hematuria, grade of hematuria, detection of viral agents and load of BK polyomavirus in urine, and; (4) HBOT-related variables - treatment profile, number of sessions, adverse effects.

The macroscopic evolution of hematuria was the parameter used to analyze the efficacy of the treatment. Clinical improvement was defined as a complete or partial response in the resolution of macroscopic hematuria. A complete clinical response was defined as the sustained absence of macroscopic hematuria for at least 2 weeks, while a partial clinical response was defined as a downgrade in the severity of cystitis. In patients with the detection of BK polyomavirus in the urine, the microbiological response was also evaluated, and it was defined as at least 1 log reduction in urinary BK viral load or viral clearance, as determined by PCR.

The ethics committees of both hyperbaric participating centers approved this study (*Comissão de Ética da Unidade Local de Saúde de Matosinhos*, *E.P.E.*; *Comissão de Ética para a Saúde*, *Hospital das Forças Armadas – Polo Lisboa*). The study was performed in accordance with appropriate ethical and regulatory standards, including obtaining informed consent from participants and/or their legal guardian(s).

Statistical analysis

A descriptive statistical analysis was performed for the collected variables, presenting the results as absolute numbers and percentages for qualitative variables and as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables.

Sequential and inferential statistical analysis was conducted comparing the group of patients with clinical response (complete or partial) to the group with no response. For inferential analysis, the *T-student* and the *Mann-Whitney U tests* were used to compare quantitative variables, and the *Chi-square* test and *Fisher's exact test* for qualitative variables. Lastly, binary logistic regression was applied to determine potential confounders and independent predictors for clinical outcomes.

The data were analyzed using *Statistical Package for the Social Sciences*, *version 28.0.1.0* (*IBM SPSS® Statistics*, USA). Statistical significance was considered for *p-values* < 0.05. Missing data were not replaced.

Results

Demographical characteristics

There were 61 patients diagnosed with late-onset HC following allogeneic HSCT who received HBOT, including 45 adults and 16 pediatric patients. Most patients were male ($n = 33$, 54.1%), and had a mean age of 28.0 (SD 14.2) years. Table 1 provides detailed patient characteristics and transplant data.

The most common nosological group observed in patients undergoing allogeneic HSCT is hematological malignancies ($n = 55$, 90.2%). Among these, the most frequent diagnosis was acute myeloid leukemia ($n = 17$, 27.9%), followed by acute lymphoblastic leukemia ($n = 13$, 21.3%) and myelodysplastic syndrome ($n = 7$, 11.5%).

All patients received allogeneic HSCT following a conditioning regimen, with 56 patients (91.8%) undergoing chemotherapy-based conditioning and 5 patients (8.2%) undergoing total body irradiation (TBI) in combination with chemotherapy conditioning. Eighteen different conditioning regimens were reported, with the busulfan plus cyclophosphamide regimen, with or without other drugs, being the most commonly used ($n = 41$, 67.2%).

Regarding the graft source, 53 patients (86.9%) received grafts from peripheral blood stem cells (PBSC), 5 patients (8.2%) from bone marrow (BM), and 3 patients (4.9%) from umbilical cord blood (UCB). Among the sample, 38 patients (62.3%) received grafts from unrelated donors and 23 (37.7%) from related donors.

Variable		*n* (%)
Age	Mean (years) Pediatric Age	28.0 (SD 14.2) 16 (26.2%)
Sex	Male Female	33 (54.1%) 28 (45.9%)
Primary diagnosis	*Malignant Hematological Pathology* Acute myeloid leukemia Acute lymphoblastic leukemia Myelodysplastic syndromes Non-Hodgkin lymphoma Chronic myeloid leukemia Hodgkin lymphoma Myeloproliferative neoplasms Acute leukemia of ambiguous lineage Multiple myeloma	55 (90.2%) 17 (27.9%) 13 (21.3%) 7 (11.5%) 6 (7.7%) 5 (8.2%) 3 (4.9%) 2 (3.3%) 1 (1.6%) 1 (1.6%)
	Non-malignant Hematological Pathology Aplastic anemia *Fanconi* anemia Paroxysmal nocturnal hemoglobinuria X-linked adrenoleukodystrophy *Shwachman-Diamond* syndrome	8 (13.1%) 3 (4.9%) 2 (3.3%) 1 (1.6%) 1 (1.6%) 1 (1.6%)
Type of conditioning	*Chemotherapy only* Busulfan, Cyclophosphamide, ATG Busulfan, Cyclophosphamide Fludarabine, Cyclophosphamide, Alemtuzumab Fludarabine, Busulfan Fludarabine, Busulfan, ATG Busulfan, Cyclophosphamide, Melphalan Fludarabine, Cyclophosphamide, ATG Cyclophosphamide Ciclosporin Melphalan Busulfan, Cyclophosphamide, Alemtuzumab Busulfan, Cyclophosphamide, Melphalan, ATG Fludarabine, Melphalan, ATG Fludarabine, Busulfan, Cyclophosphamide, ATG	56 (91.8%) 25 (41.0%) 12 (19.7%) 3 (3.8%) 3 (4.9%) 2 (3.3%) 2 (3.3%) 2 (3.3%) 1 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%)
	TBI based Cyclophosphamide, ATG, TBI Cyclophosphamide, TBI Cyclophosphamide, Alemtuzumab, TBI Cytarabine, Cyclophosphamide, TBI	5 (8.2%) 2 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%)
Stem cell source	Peripheral Blood Stem Cells Bone Marrow Umbilical Cord Blood	53 (86.9%) 5 (8.2%) 3 (4.9%)
Type of donor	Unrelated Donor Related Donor	38 (62.3%) 23 (37.7%)
Acute GvHD grade	Grade A Grade B Grade C Grade D Without Acute GvHD	6 (9.8%) 33 (54.1%) 14 (23.0%) 2 (3.3%) 6 (9.8%)
Time between HSCT and onset of HC	Median (days)	33.0 (IQR 10.0–31.0)
HC degree	Grade II Grade III	42 (68.9%) 19 (31.1%)
Virus identification in urine*	BK polyomavirus Adenovirus CMV No virus identification	56 (91.8%) 16 (26.2%) 3 (4.9%) 2 (3.3%)
Antiviral agent	Cidofovir Ribavirin Cidofovir and ribavirin	14 (23.0%) 3 (4.9%) 2 (3.3%)

Table 1. Details of clinical characteristics of the patients ($n=61$), allogeneic hematopoietic stem cell transplantation and hemorrhagic cystitis. ATG - anti-thymocyte globulin, TBI - total body irradiation, GvHD - graft-versus-host disease, HSCT - hematopoietic stem cell transplantation, HC - hemorrhagic cystitis, CMV - cytomegalovirus, IQR - interquartile range. * the number of viral agents exceed the sample number once several viral agents have been identified in the same individuals.

The median time interval between HSCT and the onset of HC was 33.0 days (IQR 10.0–31.0). The clinical severity of HC was classified as grade II in 42 patients (68.9%) and grade III in 19 patients (31.1%). Viral DNA was identified in the urine of 96.7% ($n=59$) of patients with HC. The viral identification in one patient was not investigated due to technical issues. The BK polyomavirus was the most frequently identified virus ($n=56$, 91.8%). Adenovirus was found in 16 (26.2%) patients and CMV in 3 (4.9%) patients. In 11 (18.0%) patients, both BK polyomavirus and adenovirus were identified, while 2 (3.3%) patients had BK polyomavirus and CMV, and another 2 (3.3%) patients had BK polyomavirus and CMV, concurrently. A total of 31.1% ($n=19$) of the patients received antiviral agents, such as cidofovir and/or ribavirin.

Variable		*n* (%)
Time between the onset of HC and the beginning of HBOT	Median (days)	17.0 (IQR 10.0–31.0)
Number of HBOT sessions	Median	17.0 (IQR 10.0–30.0)
HBOT treatment profile	2.1 ATA, 90' 2.4 ATA, 90' 2.4 ATA, 80' 2.5 ATA, 90'	13 (21.3%) 19 (31.1%) 6 (9.8%) 23 (37.7%)
Clinical response to HBOT	Complete response Partial response No response	44 (72.1%) 9 (14.8%) 8 (13.1%)
Microbiological response to BK polyomavirus after HBOT	Microbiological response No response	34 (63.0%) 20 (37.0%)
HBOT adverse events	Oxygen toxicity seizure Pressure intolerance Middle ear barotrauma Confinement anxiety Intolerance to the helmet Abdominal pain	1 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%) 1 (1.6%)

Table 2. Details of clinical characteristics of hyperbaric oxygen therapy. HC - hemorrhagic cystitis, HBOT - hyperbaric oxygen therapy, ATA - atmosphere absolute pressure, IQR - interquartile range.

Variable		Complete or partial clinical response ($n=53$)	No clinical response ($n=8$)	*p*-value
Age	Mean (years)	27.5 (SD 14.1)	36.9 (SD 13.3)	0.08
Sex	Male Female	29 (54.7%) 24 (45.3%)	4 (50.0%) 4 (50.0%)	0.55
Time between the onset of HC and the beginning of HBOT	Median (days)	18.0 (IQR 10.5–33.0)	11.5 (IQR 7.8–28.5)	0.39
Number of HBOT sessions	Median	19.0 (IQR 10.0–32.0)	6.0 (IQR 4.3–20.5)	<0.05
	<10 sessions ≥ 10 sessions	14 (26.4%) 39 (73.6%)	5 (62.5%) 3 (37.5%)	<0.05
HBOT treatment profile	2.1 ATA, 90' 2.4 ATA, 90' 2.4 ATA, 80' 2.5 ATA, 90'	12 (22.6%) 16 (30.2%) 5 (9.4%) 20 (37.7%)	1 (12.5%) 3 (37.5%) 1 (12.5%) 3 (37.5%)	0,91

Table 3. Comparative analysis between patients who exhibited a clinical response (complete or partial response) to those who did not respond. HC - hemorrhagic cystitis, HBOT - hyperbaric oxygen therapy, ATA - atmosphere absolute pressure, SD - standard deviation, IQR - interquartile range.

Hyperbaric oxygen therapy

All patients received HBOT as an adjunctive therapy to standard conservative treatments, with a median time interval between the onset of macroscopic hematuria and the initiation of HBOT sessions of 17.0 days (IQR 10.0–31.0). The treatment profiles varied among the patients, with 13 individuals (21.3%) receiving 90-minute sessions at 2.1 ATA, 6 (9.8%) 80-minute at 2.4 ATA, 19 (31.1%) 90-minute sessions at 2.4 ATA, and 23 (37.7%) 90-minutes sessions at 2.5 ATA. The characteristics of HBOT are presented in Table 2.

The incidence of adverse events was 9.8% ($n=6$), leading to suspending of HBOT sessions for 2 patients. One patient experienced an oxygen toxicity seizure, while another exhibited pressure intolerance. Additional adverse events reported included pressure equalization problems within the middle ear, confinement anxiety, intolerance to the helmet, and abdominal pain.

Outcomes of hyperbaric oxygen therapy

A complete response was achieved in 44 (72.1%) patients, while a partial response was observed in 9 (14.8%), giving an overall success rate of 86,9%. The median number of HBOT sessions for patients with a complete response was 15.5 sessions (IQR 10.0-26.8). The median time to clinical response was 26.5 days (IQR 14.0–57.0).

The group of patients with clinical response (partial or complete response) shows a higher number of sessions (19.0 vs. 6.0 sessions, $p\text{-value} < 0.05$). Furthermore, patients who received at least 10 sessions have a significantly higher overall success rate of 73.6% ($p\text{-value} < 0.05$). The comparative analysis between patients who exhibited a clinical response and those who did not is presented in Table 3.

There was no clinical response in 8 (13.1%) patients, although 6 interrupted treatments prematurely. A total of 6 patients (9.4%) discontinued HBOT early due to opportunistic infections ($n=2$, 3.3%), adverse events related to HBOT ($n=2$, 3.3%), cancer progression ($n=1$, 1.6%), worsening acute GvDH ($n=1$, 1.6%), and another patient for unspecified reasons. Only 2 patients suspended the HBOT due to a lack of clinical benefit after 24 and 33 sessions.

Among patients with detectable BK polyomavirus in the urine before starting HBOT ($n=56$, 91.8%), only 54 patients had their viral load reassessed after the end of the HBOT protocol. Among these, 63.0% ($n=34$)

Variable		Multivariate analysis		
		Odds Ratio	95% Confidence Interval	*p-value*
Age		0.94	0.88–1.01	0.10
Sex	Male	0.97	0.16–5.78	0.98
Time between the onset of HC and the beginning of HBOT		1.01	0.96–1.06	0.71
Number of HBOT sessions	≥ 10 sessions	12,54	1.89–83.20	< 0.05
HBOT treatment profile	2.5 ATA, 90'	0.65	0.10–4.38	0.66

Table 4. Multivariable logistic regression analysis of variable related to complete or partial response to HBOT. HC - hemorrhagic cystitis, HBOT - hyperbaric oxygen therapy, ATA - atmosphere absolute pressure.

Reference	Inclusion criteria	Sample	HBOT treatment profile	HBOT sessions	Response rate	Adverse effects rate
Cesaro S et al. (2003)[7]	HC after HSCT in paediatric patients	14	2.5 ATA, 110'	Median 17 [4–38] days	CR 78.5%	0%
Yenerel MN et al. (2009)[8]	HC after allogeneic HSCT	7	2.5 ATA, 120'	Median 40 [35–60] sessions in patients with CR	57.1%	14.3%
Savva-Bordalo et al. (2012)[2]	BK-virus-associated HC after allogeneic HSCT	16	2.1 ATA, 90'	Median 13 [4–84] sessions in patients with CR	CR 94.0%	25.0%
Zama D et al. (2013)[9]	Late-onset HC after HSCT in pediatric patients	10	2.2 ATA, 107'	Median 10 [8–30] sessions	CR 70%	NA
Costa D et al. (2015)[21]	Late-onset HC after HSCT	17	2.5 ATA, 90'	Median 20 [4–51] sessions	CR 82%	NA

Table 5. Retrospective studies on the effectiveness of HBOT in the treatment of HC after HSCT described in English literature - hemorrhagic cystitis, HBOT - hyperbaric oxygen therapy, ATA - atmosphere absolute pressure, CR - complete response, NA - data not available.

presented a microbiological response, indicating a decreased BK polyomavirus load. Additionally, one patient reduced BK polyomavirus load, although not achieving 1-log reduction. However, 25.9% ($n = 14$) experienced worsening or persistence of BK polyomavirus viral loads, although their macroscopic hematuria resolved.

Predictive factors for successful outcome with hyperbaric oxygen therapy

Additionally, the multivariable analysis identified the number of sessions equal to or greater than 10 sessions as the only predictive factor for therapeutic success (odds ratio 12.54, 95% confidence interval 1.89–83.20, *p-value* < 0.05). The investigated predictive factors are presented in Table 4.

Discussion

In our retrospective study, the overall response rate of HBOT as an adjunctive therapy in late-onset HC after allogeneic HSCT is 86.9%. In the literature, response rates for conservative treatment vary significantly. For instance, studies have reported response rates ranging from 26 to 89% for conservative treatment such as continuous bladder irrigation, hydration, and antiviral therapy[1–8]. Although our cohort includes patients with grades II or III HC who received conservative treatment and were refractory to standard care, precluding direct comparisons, the overall findings reinforce the potential of HBOT to provide superior clinical activity. This suggests that HBOT may complement treatment protocols for late-onset HC, particularly in cases refractory to standard conservative treatment.

Five retrospective studies with small sample sizes and various case series suggest that HBOT effectively manages HC after HSCT[2,8–22]. Our data are consistent with the results of the four retrospective studies, reporting a complete response rate ranging from 57 to 94% (Table 5). However, the lack of prospective randomized controlled trials limits the strength of recommendations for its use.

The effectiveness of HBOT in radiation-induced HC has already been established, with response rates ranging from 27.2 to 100%[23–32]. It is currently considered a potential treatment for radiation-induced hemorrhagic cystitis by the *European Committee for Hyperbaric Medicine* (recommendation grade I/evidence level B) and the *Undersea & Hyperbaric Medical Society*[33,34]. The rationale behind using HBOT is based on its ability to create an interchange between hyperoxygenation and periods of relative hypoxia. This creates an oxygen gradient between healthy tissue and damaged urothelium, promoting angiogenesis, fibroblast proliferation, and vasoconstriction, all essential for tissue repair. Relative hypoxia attracts macrophages to the damaged urothelial mucosa and releases growth factors, such as vascular endothelial growth factor (VEGF), that promote capillary proliferation. Hyperoxia, on the other hand, stimulates fibroblast proliferation, collagen formation, and activation of leukocytes. Additionally, nitric oxide (NO) downregulation leads to vasoconstriction and reduces edema. Due to the high levels of oxygen released in hyperbaric conditions, vasoconstriction does not worsen ischemia[35,36]. Therefore, among the available treatments for HC, HBOT is the only one that promotes angiogenesis and tissue healing[37].

Currently, there are no predictive factors for treatment response. However, in our cohort study, a number of sessions equal or greater than 10 were associated with more favorable response rates. Moreover, HBOT was

continued until macroscopic hematuria disappeared, with a mean of 15.5 sessions required for a complete response. Nonetheless, only 2 patients discontinued the treatment due to a lack of clinical benefit.

HBOT carries some risks. According to Zhang et al., their meta-analysis reported an adverse effects rate of 30.1% for HBOT, with a higher incidence among patients who underwent more than 10 sessions and those subjected to a therapeutic profile with a chamber pressure above 2.0 ATA[37]. In our sample, the rate of adverse effects is 9.8%, demonstrating good tolerance even in the pediatric cohort. Only one major complication was observed, namely an oxygen toxicity seizure. HBOT involves a risk of central nervous system oxygen toxicity, including seizures. However, these events are typically self-limiting and resolve with a reduction of the inspired partial pressure of oxygen without causing lasting effects. Costa DA et al. report an overall oxygen seizure rate of less than 0.03% in a sample that includes an analysis of 20-years and over 180,000 HBOT sessions. Frequency increases longitudinally after a median of 21 HBOT treatment sessions. However, the median number of sessions for a complete response of late-onset HC after allogeneic HSCT in our sample is relatively low (median of 15.5 sessions). Moreover, incorporating a 5-minute air-break interval (a 5-minutes period with FiO2 of 21%) in the treatment protocols appears to be associated with a decrease in the frequency of seizures[38].

Limitations and challenges regarding the use of HBOT include availability, treatment duration, costs, and contraindications[3,5,39]. Utilizing HBOT requires access to specialized centers equipped with hyperbaric chambers and trained healthcare professionals. The limited availability of such centers, especially in some geographical regions, can restrict patients' access to this therapy. The time commitment is also significant considering the need for more than 10 sessions, lasting more than one hour per session. Another consideration is the cost associated with HBOT. Although, it should be compared to the potential economic burden of prolonged hospitalization with multiple transfusions and/or urological surgeries. Furthermore, specific contraindications to HBOT need to be taken into account. Patients with pre-existing medical conditions such as obstructive pulmonary diseases, pulmonary bullae, recent thoracic surgery, a history of recent and uncontrolled seizures, or claustrophobia may not be suitable candidates for HBOT. However, it is essential to note that most contraindications are relative rather than absolute. The decision to proceed with HBOT should involve carefully assessing the potential risks and benefits, considering the patient's conditions and circumstances.

Our study's primary limitation is the lack of a comparative arm, which restricts the ability to draw definitive conclusions about HBOT's efficacy compared to standard care alone. Additionally, the study's retrospective nature introduces potential biases, such as incomplete clinical records, which can affect the accuracy and comprehensiveness of the collected data. There is also a potential for analysis-by-responder bias, as patients who tolerated HBOT well or were more likely to respond positively may have continued treatment for extended periods. Furthermore, the study did not include follow-up data after patient were discharged from hyperbaric medicine centers, limiting the ability to assess long-term outcomes and the sustainability of the treatment benefits. Future randomized controlled trials are necessary to mitigate these biases and provide more conclusive evidence.

However, conducting a randomized, controlled, and double-blind clinical trial for HBOT in treating late-onset HC presents significant challenges. As *Lansdorp* and *Van Hulst* (2018) detailed, researchers could utilize a sham-controlled design. This approach involves methods such as lower pressure with 21% FiO_2, the same pressure with adjusted FiO_2 levels, or the same pressure with 21% FiO_2, ensuring adequate blinding[40]. *Louge* et al. (2023) also validate a sham treatment using the lowest atmospheric pressure (1.3 ATA) combined with the additional blinding strategies of forced ventilation, enclosure heating, and rapid compression in five minutes to simulate a therapeutic compression Table[41]. Given the rarity of late-onset HC, achieving a sufficiently large sample size would require many years, as evidenced by the 25-years of our current study. To counter this limitation, collaboration of multiple centers is required to enroll sufficient patients within a reasonable timeframe. Additionally, the ethical considerations of administering a sham treatment to critically ill patients complicate the study design, as it involves withholding potentially beneficial therapy from the control group. Despite the absence of high-level evidence, the resolution of hematuria in most retrospective studies with HBOT may support recommendations for its use as a treatment strategy for HC. Moreover, HBOT has been recognized as a therapeutic option in the *ECIL* (recommendation level CIII)[3].

In conclusion, our study provides evidence supporting the efficacy and safety of HBOT as an adjunctive treatment for late-onset HC after allogeneic HSCT. However, to establish the definitive efficacy and safety of HBOT in the treatment of late-onset HC, further prospective, randomized, and well-controlled clinical trials are warranted.

Future perspectives in the field of HBOT for late-onset HC after allogeneic HSCT involve not only conducting well-designed clinical trials but also optimizing treatment protocols, long-term follow-up studies, physiopathology mechanistic investigations, identification of predictive factors, and cost-effectiveness analysis. Advancements in these areas will contribute to a better understanding of HBOT's role in managing late-onset HC and help guide evidence-based treatment decisions in the future.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due ethical or legal restrictions but are available from the corresponding author on reasonable request.

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Authors' contributions
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Declarations

Competing interests
The authors declare no competing interests.

Additional information
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