BMC Pediatrics

RESEARCH

Open Access

Pulmonary function testing in pediatric allogeneic stem cell transplant recipients to monitor for Bronchiolitis obliterans syndrome: a systematic review

William A. Gower[1*], Maximiliano Tamae-Kakazu[2], Shivanthan Shanthikumar[3,4,5], Saumini Srinivasan[6,7], Erin E. Reardon[8], Amisha V. Barochia[9], Edward Charbek[10], Charlotte Calvo[11,12], Pi Chun Cheng[13,14], Shailendra Das[15], Stella M. Davies[16,17], Jessica Gross[18], Ajay Sheshadri[19], Christoper T. Towe[17,20], Samuel B. Goldfarb[21,22] and Narayan P. Iyer[23]

Abstract

Background Bronchiolitis obliterans syndrome (BOS) represents a significant source of morbidity and non-relapse mortality among children and young adults treated with allogeneic hematopoietic stem cell transplantation (aHSCT). Pulmonary function testing (PFT) pre- and post-aHSCT may allow for pre-symptomatic detection of BOS, and thus early intervention. Current guidelines and practices vary regarding which tests to perform and timing relative to transplant. A systematic review evaluating PFT before and after pediatric aHSCT was conducted to inform American Thoracic Society clinical practice guidelines on detection of BOS.

Objective To determine the optimal approach to conducting PFT prior to and after pediatric aHSCT.

Study Design We performed a systematic review of the literature to identify studies of PFT in human aHSCT recipients < 25 years of age to address two questions: (1) *Should pre-transplant screening PFT be performed in pediatric patients who will undergo aHSCT?* (2) *At what frequency should pediatric patients who have had aHSCT undergo PFT?* We searched in Medline through August 2022 for studies that enrolled patients < 25 years of age being treated with aHSCT for whom PFT data were reported before or after transplant.

Results The 30 studies with pre-transplant PFT data showed a wide range of findings, with the majority demonstrating abnormalities. In studies reporting respiratory symptoms, 85–100% of patients were asymptomatic. In the 21 studies reporting post-transplant PFT, 11 used a surveillance strategy where at least one test was performed in the first year post-transplant. Median time to BOS diagnosis was 6–12 months in the regular surveillance studies, and 6–24 months in the others. Forced expiratory volume in one second at the time of BOS diagnosis was 38–84% predicted in studies with regular surveillance versus 44–57% predicted in studies with no surveillance. In the surveillance group, BOS was identified in some patients who were asymptomatic. Data quality in studies reviewed was moderate to very low.

*Correspondence:
William A. Gower
gower@email.unc.edu

Full list of author information is available at the end of the article

Conclusions Abnormalities in PFT are common in children prior to aHSCT. Regular monitoring in the first 1–2 years post-aHSCT may improve early and/or pre-symptomatic identification of BOS, but significant limitations may still be seen at the time of diagnosis. Higher quality data are needed.

Keywords Bronchiolitis obliterans syndrome, pediatrics, Stem cell transplantation

Background

Allogeneic hematopoietic stem cell transplantation (aHSCT) is an important modality for treating hematologic malignancies as well as many non-malignant conditions in children and young adults. Pulmonary complications are relatively common after pediatric aHSCT and cause significant morbidity and mortality [1–5]. Bronchiolitis obliterans, in which immune-mediated injury to the small- and medium-sized airways results in worsening irreversible obstruction with air trapping, is the primary pulmonary manifestation of chronic graft versus host disease (cGVHD) after aHSCT [6]. As lung biopsy may be associated with morbidity in this population [7–9], bronchiolitis obliterans syndrome (BOS), based on clinical criteria, is used as proxy. Current diagnostic criteria for BOS are based primarily on post-transplant changes in lung function as measured by spirometry, with supporting features from chest imaging and static lung volumes [10]. As with the form of BOS seen in lung transplant recipients with allograft rejection [11], BOS due to cGVHD can be associated with rapid clinical decline [6].

Under current National Institutes of Health consensus criteria [10], pulmonary function testing (PFT) is required to diagnose BOS. This is established by (1) forced expiratory volume in one second (FEV1) < 75% predicted and an irreversible decline ≥ 10% in under two years, (2) ratio of FEV1 to vital capacity < 0.7 or below the lower limit of the 90% confidence interval, (3) absence of infection, and (4) either: (a) cGVHD in at least one organ system, or air trapping evidenced by (b) expiratory chest computed tomography, or (c) residual volume (RV) > 120% predicted or RV/total lung capacity (TLC) > 90% confidence interval.

Monitoring aHSCT recipients with serial PFT allows for objective longitudinal assessment, with the goal of identifying pre-symptomatic BOS. A greater impairment in lung function at the time of diagnosis has been associated with worse outcomes in cohort studies including mostly adult transplant recipients [12, 13]. Although currently available therapies for BOS are somewhat limited [14], evidence from adult studies suggests that early intervention could potentially arrest or slow decline in lung function with improved outcomes [13, 15, 16]. While all current pediatric guidelines recommend PFT surveillance in aHSCT recipients, the recommended frequency ranges from every three months to annually in the first year post-transplant, with variability in which specific tests are recommended [17–20]. Additionally, practice patterns vary across pediatric transplant centers [21].

In 2022-23, an American Thoracic Society (ATS) working group prepared clinical practice guidelines on the detection of bronchiolitis obliterans in pediatric aHSCT patients [22]. Two of the questions addressed by these guidelines relate to the timing of PFT and specific tests to be performed prior to and after aHSCT. The following systematic review was completed to inform the guideline committee's recommendations regarding these questions.

Methods

We synthesized the best available evidence for the following two Population, Intervention, Comparator, and Outcome (PICO) questions:

1. Patients: Children and young adults (< 25 years of age) scheduled to undergo aHSCT.

Intervention: Pre-transplant PFT using spirometry, measurement of static lung volumes, or diffusion capacity for carbon monoxide (DLCO).

Comparator: No PFT.

Outcomes: Diagnostic yield (abnormal PFT), BOS diagnosis post-transplant, BOS severity at diagnosis, post-transplant mortality.

2. Patients: Children and young adults (< 25 years of age) who underwent aHSCT.

Intervention: Post-transplant surveillance PFT (at least two tests in the first 12 months after aHSCT) using spirometry, measurement of static lung volumes, or DLCO.

Comparator: No surveillance PFT.

Outcomes: Diagnostic yield (abnormal PFT), timing of BOS diagnosis, BOS severity at diagnosis, mortality, supplemental oxygen use.

Electronic literature searches were conducted by a medical librarian. Standard methodology for conducting systematic reviews as per guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions were followed [23]. Search results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

Study identification and eligibility

Study identification and eligibility criteria were developed and documented in a search strategy (Table 1) using the PICO framework as described in the Cochrane

Table 1 Search strategy utilized to identify the 2003 abstracts selected for full-text review

1	exp Pediatrics/ or exp Infant/ or exp Child/ or exp Adolescent/	3,896,875
2	(pediatric* or infant* or baby or babies or child or children or adolescent* or teen*).ti, ab, kw, kf.	2,118,118
3	1 or 2	4,377,917
4	exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation/	135,602
5	((bone marrow or stem cell) adj3 (transplant* or graft*)).ti, ab, kw, kf.	95,124
6	4 or 5	164,354
7	exp Lung Diseases/ or exp Respiratory Function Tests/	1,309,370
8	((bronchiolit* adj2 (obliteran* or obliterative* or constrictive* or exudative* or proliferative*)) or (pulmonary adj2 (graft versus host or graft vs. host)) or (lung adj2 disease*) or ((lung or pulmonar* or respirator*) adj2 function test*) or airway resistan* or blood gas analysis or oximetry or bronichial provocation or capnography or lung compliance or lung volume measure* or total lung capacit* or maximal respiratory pressure* or plethysmography or pulmonary gas exchange or pulmonary diffusing capacit* or ventilation-perfusion ratio* or forced expiratory flow rate* or forced expiratory volume* or maximal voluntary ventilat* or spirometr* or bronchospirometr* or valsalva maneuver or ventilation-perfusion scan* or work of breathing or DLCO or diffusion capacit* or diffusing capacit* or transfer factor* or residual volume* or multiple breath washout or lung clearance index or inert gas washout or ((peripheral airway* or small airway*) adj2 (disease* or function*))).ti, ab, kw, kf.	180,549
9	7 or 8	1,364,529
10	3 and 6 and 9	2003

Handbook [23]. We performed literature searches in July-August 2022 in Medline (via OvidSP) to identify studies describing pulmonary function testing in children and young adults undergoing aHSCT transplantation. In addition to bibliographic databases, a manual search was performed on the reference lists of identified eligible studies, and the guideline panelists were asked to identify additional studies that may be relevant which were not identified in the search.

Study screening and ascertainment of eligibility

Eligibility criteria were developed by the project team and checked by the lead methodologist. Before the screening began, duplicate studies and those that did not meet language or date restrictions were excluded. The screening procedure was conducted in a two-step process: (1) title/abstract screening and (2) full-text screening. Title/abstract screening was conducted by two screeners using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and checked by the lead methodologist. Full-text screening was conducted by two independent reviewers. Discrepancies between reviewers were identified and resolved by an independent third reviewer.

We included observational studies that reported results of PFT before or after the transplantation of any follow-up duration. We only included studies reported as full text articles. Conference abstracts were not included in this review. We included studies of patients < 25 years of age who were either scheduled for or received aHSCT. Studies of adult and pediatric patients where data from children and young adults were separately reported were also included. We did not exclude any primary conditions leading to aHSCT.

Data extraction

Data from relevant studies were extracted using a specifically developed standardized data extraction form. For each trial, study, patient, and treatment characteristics, as well as PFT results, and data about BOS were extracted. For cohort studies, the proportion of patients diagnosed with PFT abnormalities prior to transplant were noted. We recorded the changes in post-transplant PFT results over time, proportion of patients diagnosed with BOS, and the symptomatology of patients at the time of BOS diagnosis.

Risk of bias assessment

Risk of bias (study quality) of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies [25]. In brief, this tool includes three domains: patient selection, comparability, and outcomes. The risk of bias for each study and the overall risk of bias for individual outcomes is reported in three categories which correspond to no serious risk, serious risk and very serious risk of bias.

Evidence tables

Evidence tables were created to summarize estimated effects on an outcome-by-outcome basis. The evidence tables were used by the guideline committee to inform clinical recommendations.

Protocol Registration

The protocol for the systematic review has been registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols [26] (registration number: INPLASY202450075, DOI:https://doi.org/10.37766/inplasy2024.5.0075). Details of the protocol

for the systematic review can be accessed at https://inplasy.com/inplasy-2024-5-0075/.

Results

For the two PICO questions, we screened 2003 abstracts. Of these, two were duplicates, and from the 2001 unique abstracts, we selected 121 for full review. We ultimately utilized 30 studies [27–56] to address PICO 1, and 21 studies [27–29, 31, 34, 37, 38, 42, 46, 48, 50, 54–63] to

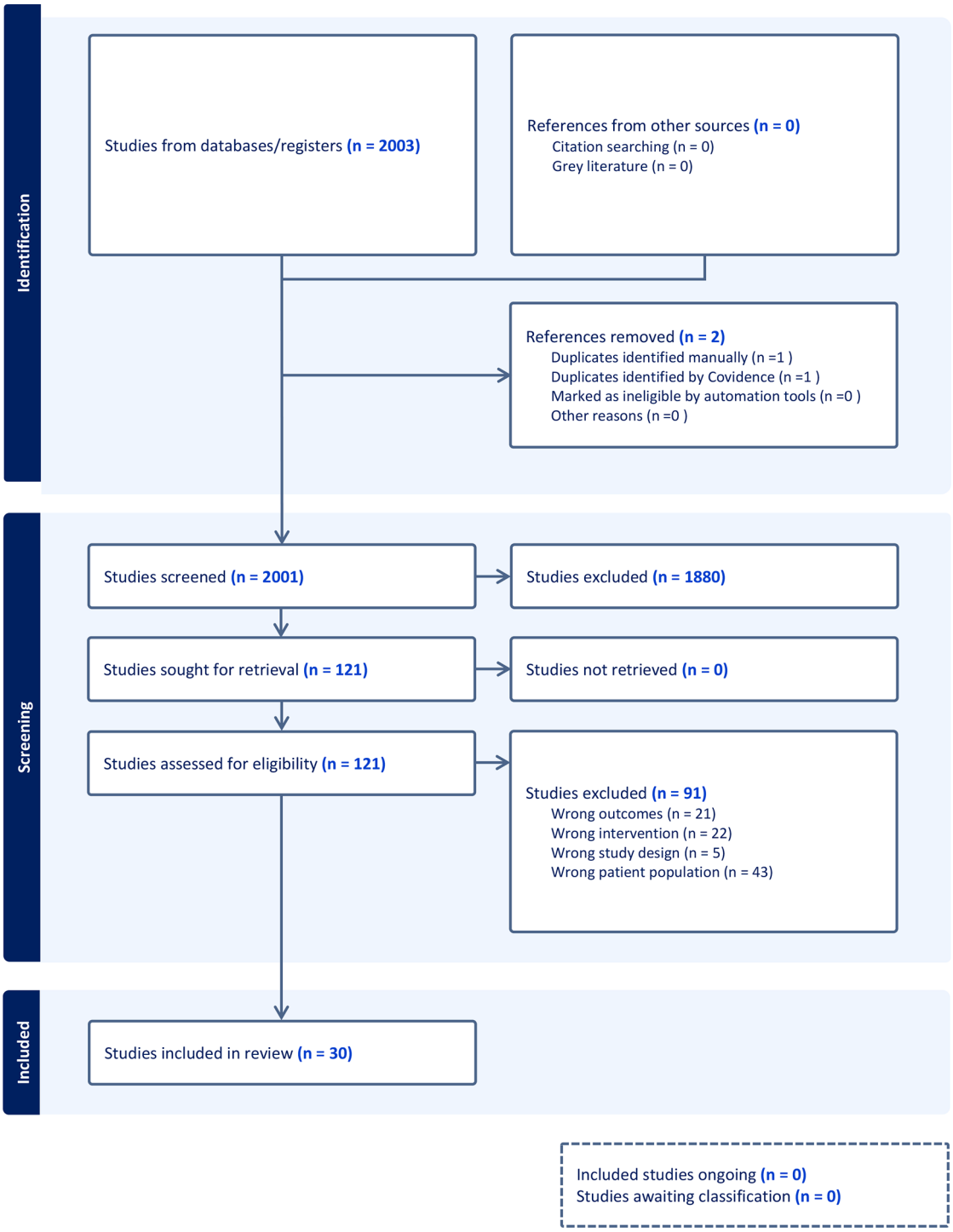

Fig. 1 PRISMA diagram illustrating selection of studies for PICO 1

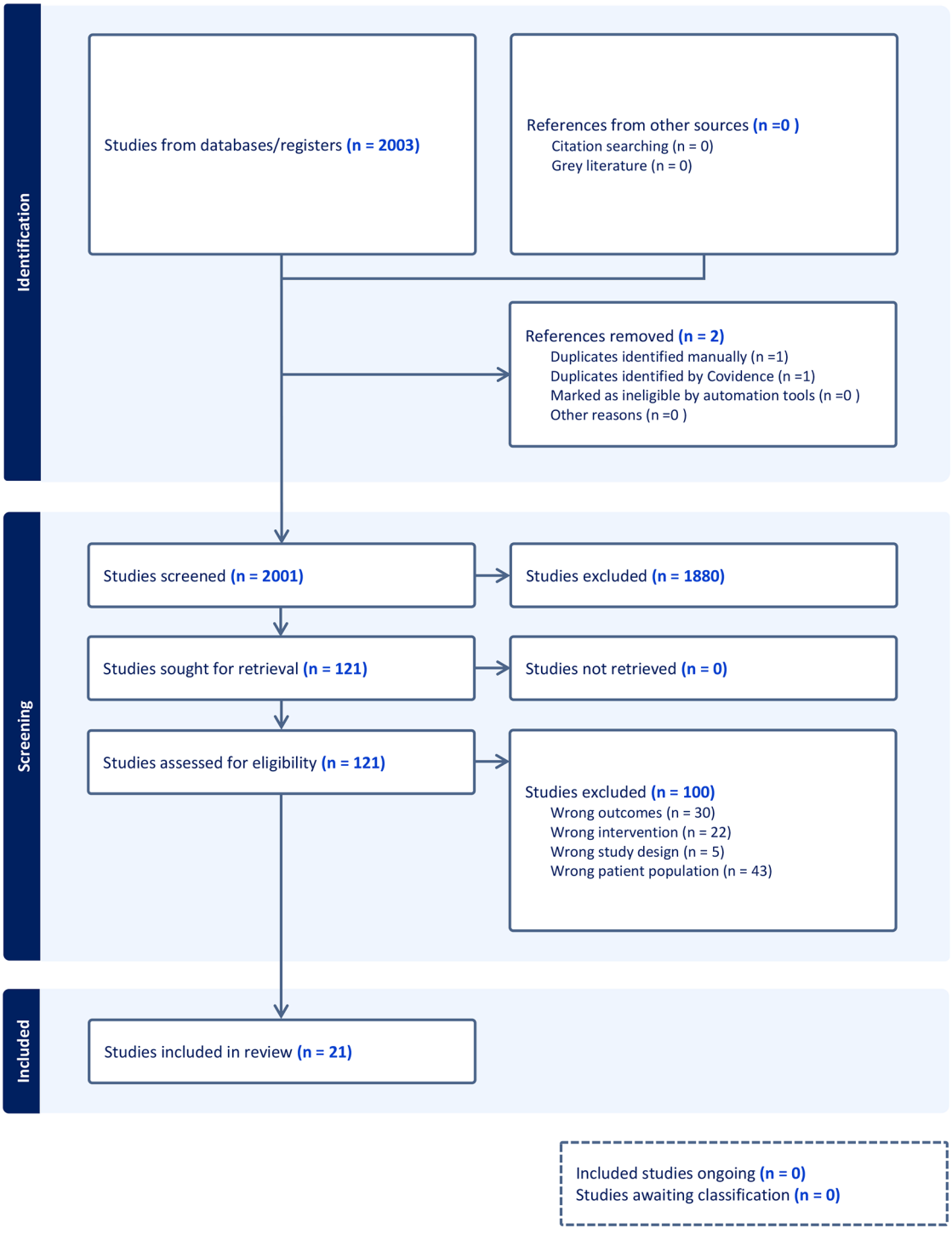

Fig. 2 PRISMA diagram illustrating selection of studies for PICO 2

address PICO 2. The PRISMA flow diagrams are illustrated in Fig. 1 (PICO 1) and Fig. 2 (PICO 2). All studies included are summarized in Table 2 (PICO 1) and Table 3 (PICO 2).

Pre-transplant testing

We gathered data on PFT results pre-aHSCT and association with development of BOS as well as the following additional clinical outcomes: post-aHSCT pulmonary complications, intensive care unit (ICU) admissions, and mortality. The studies selected included patients who underwent any type of aHSCT -- most received bone

Table 2 Summary of the 30 studies included for PICO 1

Study Design Location Years	Number of subjects	Population enrolled	Key results
Alonso-Riofrio 2004 Cohort Spain 1992–2002	77	Patients surviving > 100 days post-aHSCT	Mean pre-aHSCT FEV1 = 97% predicted
Bruno 2004 Cohort France 1984–2000	80	Children receiving aHSCT	Only change in spirometry from baseline to 2 yrs reported
Duncan 2008 Cohort US 2001–2005	216	Children receiving aHSCT	Mean pre-aHSCT: FEV1 = 99% predicted FEV1/FVC = 90% predicted
Friedman 2021 Cohort US 2012–2017	19	Children with sickle cell disease 2 to 21-yo receiving aHSCT	Pre-aHSCT: 7 patients (41%) had FEV1 < 80% predicted, 3 (18%) had an FEV1/FVC < 0.80, 2 (12%) had a TLC < 80% predicted, and 11 (65%) had DLCO < 80% of predicted
Gassas 2013 Cohort Canada 2009–2011	39	Children receiving aHSCT	Mean pre-aHSCT FEV1 = 95% predicted
Inaba 2010 Cohort US 1990–2005	89	Children receiving aHSCT	Pre-aHSCT abnormalities (prevalence): FEV1 = 22%, FEV1/FVC = 18%, FEF25-75% = 17%, FVC = 16%, TLC = 12%, DLCO = 19%
Isgro 2017 Cohort Nigeria 2010–2015	37	Children with sickle cell disease receiving aHSCT	Pre-aHSCT: 11/25 (44%) had restrictive pattern 18/25 (72%) had reduced FEV1
Jung 2021 Cohort South Korea 2006–2017	21	Children with post-aHSCT BOS	Pre-aHSCT mean ± SD: FEV1 = 93 ± 13% predicted FVC = 88 ± 15% predicted FEF25-75% = 113 ± 24% predicted
Kaplan 1992 Cohort US 1977–1988	46	Children receiving mostly aHSCT whose long- term PFT data were available	Pre-aHSCT < 80% predicted: FVC = 24%, FEV1 = 27%, and FEV1/FVC = 29%
Kaplan 1994 Cohort (divided into aplastic anemia and malignancy) US 1977–1988	46	Children receiving mostly aHSCT whose long- term PFT data were available	Pre-aHSCT < 80% predicted: FVC = 6–9%, FEV1 = 13–27%, FEV1/FVC = 9–20%, FEF25-75% = 3–9%
Kaya 2009 Cohort US 1996–2006	110	Children receiving aHSCT	Pre-aHSCT abnormalities: FVC = 19%, FEV1 = 20%, FEV1/FVC = 13%, TLC = 9%, DLCO = 58%
Kim 2021 Cohort South Korea 2009–2017	46	Children post-aHSCT with obstructive lung disease	Pre aHSCT mean ± SD: FEV1 = 105% ± 25% (unfavorable prognosis) FEV1 = 106% ± 15% (favorable prognosis)
Lee 2021 Cohort Korea 2010–2018	176	Children > 6-yo receiving aHSCT for malignant disease	Pre-aHSCT $DLCO_{adj}$ was significantly lower in the non-relapse mortality (NRM) group compared to disease-related mortality (DRM) group (survivors = 76 ± 13%; DRM = 78 ± 15%; NRM = 62 ± 14%; $p = 0.02$)

Table 2 (continued)

Study Design Location Years	Number of subjects	Population enrolled	Key results
Madanat-Harjuoja 2014 Cohort Finland 1993–2005	51	Children > 6-yo receiving aHSCT	8 (16%) patients had an abnormal baseline PFT, 5 restrictive and 3 mild obstructive changes (all diagnosed with asthma) Prior to aHSCT, mean FVC = 93% predicted (range 60–121) and median was 92%; mean FEV1 = 95% (range 74–116) and median was 95%; mean FEV1/FVC = 0.98 (0.79–1.00) Patients with abnormal pre-aHSCT spirometry result were at increased risk of abnormal spirometry result following transplant (HR 4.82, 95% CI 1.02 – 22.84)
Nysom 1996 Cohort Denmark Before 1990	25	Children receiving aHSCT	Almost all had below normal pre-aHSCT FEV1/FVC, FVC, or DLCO
Park 2011 Cohort South Korea 2002–2009	127	Children receiving aHSCT	Mean pre-aHSCT FEV1 = 101% predicted
Piesiak 2013 Cohort Poland 2007–2010	23	Children/adults receiving aHSCT	6/23 (26%) had abnormalities: 4 in DLCO, 1 obstructive, and 3 restrictive Mean pre-aHSCT percent predicted: FEV1 = 81%, FVC = 87%, FEV/FVC = 84%, DLCO = 85%, TLC = 81%, RV = 121%
Prais 2014 Cohort Israel 1998–2008	57	Children > 6-yo receiving mostly aHSCT	27% had abnormal pre-transplant spirometry: 9% obstructive, 7% restrictive, 11% isolated diffusion abnormality Mean percent predicted values FEV1 = 91%, FVC = 87%, FEV1/FVC = 91%, FEF25-75 = 105%, DLCO = 88%
Quigg 2012 Cohort US 2001–2006	41	Children 5 to 19-yo receiving aHSCT	71% had one or more abnormal PFT parameters pre-aHSCT: 22% obstructive, 34% low $DLCO_{adj}$ and $DLCO_{adj}$/VA
Sanchez 1997 Cohort Spain 1981–1995	20	Children post-aHSCT with obstructive lung disease	Normal spirometry before aHSCT

Table 2 (continued)

Study Design Location Years	Number of subjects	Population enrolled	Key results
Srinivasan 2014 Cohort US 1990–2009	410	Children receiving aHSCT	Abnormal spirometry pre-aHSCT: FEV1 = 15% (7% had FEV1 < 70% predicted), FVC = 16% (6% had FVC < 70% predicted), FEF25-75% = 28% (13% had FEF25-75% <70% predicted), TLC 29% (12% had TLC < 70% predicted). 3% DLCO was < 50% predicted 5% had obstructive pattern, 27% restrictive pattern, 2% mixed Logistic regression analysis: each unit decrease in FEF25–75% resulted in a threefold increased risk of developing pulmonary complications ($P = 0.02$) Multivariate analysis: RV < 50% predicted, FRC < 50% predicted, TLC < 50% predicted, and T-cell depletion predicted death due to pulmonary complications Multivariate analysis: FEV1 < 70% predicted, FVC < 70% predicted, TLC < 60% predicted, RV < 50%, and the presence of restrictive pattern associated with poor survival
Srinivasan 2017 Cohort US 1990–2009	410	Children receiving aHSCT	Only change in spirometry from baseline reported
Uderzo 2007 Cohort Italy 1994–1997	162	Children receiving aHSCT	21/99 (21%) had abnormal pre-aHSCT spirometry
Uhlving 2013 Cohort Denmark 1990–2010	130	Children receiving aHSCT	Pre-aHSCT FEV1 abnormal in 26%
Uhlving 2015 Case-control Denmark 2002–2009	128 (64 cases)	Cases: children < 16-yo receiving aHSCT Controls: healthy children/adults	Only change in spirometry from baseline reported
Uhlving 2019 Cohort Denmark 2010–2012	30	Children between 3 to 16-yo who underwent aHSCT	Pre-aHSCT: 13% abnormal FEV1, 70% abnormal DLCO Abnormal FEV1 pre-aHSCT gave OR of 12.0 (95% CI 0.8-177.4) for developing BO/BOS
Versluys 2015 Cohort Netherlands 2008–2013	142	Children who underwent aHSCT	66% had pre-aHSCT spirometry Mean pre-aHSCT percent predicted: FEV1 = 83%, FVC = 87%, TLC = 86%, DLCO = 81%
Walther 2020 Cohort Germany 2000–2017	14	Children with post-aHSCT BOS	Spirometry normal before aHSCT
Wieringa 2005 Cohort Netherlands 2001–2003	39	Children undergoing aHSCT	Only change in spirometry from baseline reported

Table 2 (continued)

Study Design Location Years	Number of subjects	Population enrolled	Key results
Yoon 2015 Cohort South Korea 2009–2012	110	Children undergoing aHSCT	Pre-aHSCT mean ± SD: FEV1 = 102 ± 16% Abnormal in 6% of patients

marrow transplantation -- and had pre-transplant PFT results reported. Not all studies used the same normative data for determining percent of predicted values, and abnormalities were defined differently across studies. Similarly, those that defined restrictive and obstructive patterns used slightly different definitions. Of the six studies that reported pre-transplant static lung volumes, one utilized gas washout [32], and the others, body plethysmography [30, 37, 43, 47, 53]. When available, we included data on the development of BOS. The age range for patients included in the selected studies was 0.3–23 years of age. The year of transplant was before 2000 for all patients in 12 studies, after 2000 for all patients in 16 studies, while two included patients transplanted both before and after 2000. Of the 37 studies used for either PICO 1 or 2 (Tables 2 and 3), 14 reported data both before and after aHSCT [27–29, 31, 34, 37, 38, 42, 46, 48, 50, 54–56].

The findings for pre-aHSCT spirometry parameters and DLCO are summarized in Table 4. Because of the wide prevalence ranges of abnormalities and retrospective cohort nature of all studies, most were determined to be of moderate quality. Most studies for PICO 1 were determined to have low risk of bias. For those that had higher risk, this was due to a lack of diversity in diagnosis requiring aHSCT, thus limiting the generalizability of the findings from these studies (Fig. 3 and Supplemental Table 1).

Spirometry All studies included reported some spirometry data. The definition of abnormal results varied between studies, but most used a threshold of < 80% of predicted value, although different reference equations were utilized. As shown in Table 4, the most commonly reported pre-aHSCT parameter was FEV1 in 16 studies [29–32, 35–37, 40, 42, 45–47, 50, 52, 54, 56]. Ten reported forced vital capacity (FVC) [32, 35–37, 40, 41, 47, 50, 54, 56], thirteen reported ratio of FEV1/FVC [27, 29, 30, 32, 35–37, 40, 41, 50, 52, 55, 56], and four reported forced expiratory flow between 25 and 75% of vital capacity (FEF25-75%) [32, 36, 47, 56].

Total lung capacity As shown in Table 4, pre-transplant TLC was reported in six studies. The mean TLC was within normal limits in one [30], and among the remaining five studies [32, 37, 41, 43, 47], the prevalence of abnormalities ranged from 9 to 29%.

Diffusion capacity Results from the ten studies reporting DLCO [30, 32, 37, 41, 43, 45, 47, 50, 52, 55] are summarized in Table 4.

Restriction and obstruction Nine studies [32, 33, 40, 43–45, 47, 48, 55] reported patterns of abnormalities, either from spirometry, static lung volumes, or both. The prevalence of a restrictive pattern ranged from 7 to 50%, obstructive pattern 0–24%, and mixed pattern 1–2%.

Respiratory symptoms Five studies [37, 52, 53, 55, 64] provided data on presence of respiratory symptoms, with 85–100% reporting no symptoms prior to transplant.

Association with BOS Association between pre-aHSCT spirometry was analyzed in seven studies [29, 34, 38, 42, 54, 56, 64] but none reported any statistically significant association between any pre-aHSCT spirometry parameter and development of BOS.

Mortality and other clinical outcomes Kaya et al. [37] found that lower pre-transplant FEV1 and/or FVC were associated with increased odds of respiratory failure leading to mechanical ventilation, with high rates of mortality among ventilated patients. Lee et al. [39] reported an association between lower pre-aHSCT hemoglobin-adjusted DLCO and higher mortality. Quigg et al. [45] found abnormal pre-aHSCT DLCO adjusted for hemoglobin and alveolar volume was predictive of mortality in univariate analysis. Srinivasan et al. [47] reported decreased FEV1, FVC, TLC, RV, and the presence of restrictive lung disease were all associated with poor survival in multivariate analysis.

Five studies examined pre-aHSCT PFT results in relation to pulmonary outcomes other than BOS, ICU admissions, and mortality, with mixed findings. One found that pre-aHSCT PFT results were not predictive of post-transplant severe obstructive lung disease or worsening changes on chest computed tomography scan [38]. Another compared patients who developed any late-onset non-infectious pulmonary complications versus those who did not, and found that pre-aHSCT PFT

Table 3 Summary of the 21 studies included for PICO 2

Study Design Location Years	Number of subjects	Population enrolled	Spirometry schedule	Key results
Alonso Riofrio 2004 Cohort Spain 1992–2002	77	Patients surviving > 100 days post-aHSCT	Pre Post: 1–3, 3–6, 6–12, and 12–24 mos	Median time to BOS diagnosis = 184 days Mean FEV1 at diagnosis = 57% predicted
Gassas 2013 Cohort Canada 2009–2011	39	Children receiving aHSCT	Pre Post: 1, 3, 6, 9, 12, 18, and 24 mos	Median time to BOS diagnosis = 192 days Mean FEV1 just prior to diagnosis = 58% predicted
Jung 2021 Cohort South Korea 2006–2017	21	Children with post-aHSCT BOS	Pre Post: every 3 mos	Mean time to BOS diagnosis = 14 mos Mean at diagnosis: FEV1 = 38% predicted, FVC = 62% predicted, FEF25-75% = 16% predicted
Kaya 2009 Cohort US 1996–2006	110	Children receiving aHSCT	Pre Post: 3, 6, 12, and 24 mos	FEV1 reduced in 46% at 3 mos, 49% at 6 mos, and 35% at 12 mos Spirometry at 3 mos predicted pulmonary complications
Kim 2021 Cohort South Korea 2009–2017	46	Children post-aHSCT with obstructive lung disease	Pre Post: 3, 6, 12, and 24 mos	At time of obstructive lung disease diagnosis: unfavorable prognosis mean FEV1 = 52% predicted, favorable prognosis = 84% predicted Median time from aHSCT to obstructive lung disease with unfavorable prognosis = 382 days, interquartile range (IQR) = 136–580 Median time from aHSCT to obstructive lung disease with favorable prognosis = 372 days, IQR = 137–571
Link 1986 Cohort Germany 1980	26	All who attended institutional follow-up post-aHSCT	Pre Post: 1–6 mos	In 3 patients with BOS, pre-aHSCT mean FEV1 = 91% predicted; after diagnosis, mean FEV1 = 46% predicted
Park 2011 Cohort South Korea 2002–2009	127	Children receiving aHSCT	Pre Post: 3 and 12 mos	Mean time to diagnosis = 259 days 2 with BOS had spirometry; post-aHSCT 3 mos FEV1 = 103% predicted, at time of diagnosis FEV1 = 46% predicted
Srinivasan 2017 Cohort US 1990–2009	410	Children receiving aHSCT	Pre Post: 3 and 6 mos, then yearly thereafter	Post-aHSCT FEV1 median change in recovery group (n = 171): 0-100 days = -0.95, 101–365 days = -1.39, > 365 days median= -1.01 Post-aHSCT FEV1 median change in 'no recovery' (n = 137): 0-100 days = -1.53; 101–365 days median = -2.38; >365 days = -2.22 BOS diagnosis time: 0-100 days 2 patients, 101–365 days 2 patients, > 365 days 1 patient
Uhlving 2013 Cohort Denmark 1990–2010	130	Children receiving aHSCT	Pre Post: 3 and 12 mos, then yearly thereafter	3–9 mos: FEV1 normal in 55% 9–18 mos FEV1 normal in 56% > 18 months: FEV1 normal in 66%
Wieringa 2005 Cohort Netherlands 2001–2003	39	Children receiving aHSCT	Pre Post: <1 year, then > 1 year	Difference in FEV1: pre-aHSCT and 1 year = -10% < 1 year and > 1 yr= -7% pre-aHSCT to > 1 year = -4%
Yoon 2015 Cohort South Korea 2009–2012	110	Children receiving aHSCT	Pre Post: 3, 6, and 12 mos	3 mos: mean FEV1 = 98% predicted, normal in 90% 6 mos: mean FEV1 = 98% predicted, normal in 91% 9 mos: mean FEV1 = 98% predicted, normal in 90% 12 mos: mean FEV1 = 97% predicted, normal in 92% Mean FEV1 at time of diagnosis = 42% predicted

Table 3 (continued)

Study Design Location Years	Number of subjects	Population enrolled	Spirometry schedule	Key results
Bruno 2004 Cohort France 1984–2000	80	Children receiving aHSCT	Pre Post: 2 and 5 yrs	Mean difference at 2 yrs: FEV1 = -8% predicted, FVC = -7% predicted One patient with BOS at 2 years
Ciki 2019 Cohort Turkey 2005–2015	195	All who attended institutional follow-up post-aHSCT	Pre Post: yearly	Progressive FEV1 decline in patients with pulmonary complications Median time to diagnosis = 9 mos (range 1-181)
Duncan 2008 Cohort US 2001–2005	216	Children receiving aHSCT	Pre Post: at 1 yr	10/18 BOS had pre-aHSCT spirometry, and 16 had PFT at time of diagnosis Mean at BOS diagnosis: FEV1 = 57% predicted, FEV/FVC = 73% predicted Median time to diagnosis = 328 days (range 48–927)
Ferry 2007 Cohort France 1985–2000	112	All patients who survived at least 1 year	Post: Yearly	Median time for lung complication with obstructive syndrome = 775 days (range 173–1587)
L'excellent 2019 Cohort France 2000–2004	35	35/90 followed up long term	Post: at some point 5–10 years	13 symptomatic patients had mean FEV1 Z-score = -2.8 5/13 diagnosed with BOS
Moutafidis 2021 Cohort Greece 2014–2019	12	Patients post-aHSCT with respiratory symptoms	Once at diagnosis/ presentation	FEV1 mean Z-score time of diagnosis = -3.6 Median time to diagnosis = 608 days
Ratjen 2005 Cohort Germany not reported	9	Patients with BOS	Pre Post: at BOS diagnosis	FEV1 normal pre-aHSCT, lowest at time of diagnosis, mild improvement after first 3 mos of treatment and stable during follow-up Mean time to diagnosis = 56 ± 80 days
Sanchez 1997 Cohort Spain 1981–1995	20	Children post aHSCT with obstructive lung disease	Pre Post: time of symptoms, then 6–12 monthly	At time of diagnosis, 35% had mild obstruction (FEV1 > 50% predicted), 35% had moderate (FEV1 30–50% predicted), 30% had severe obstruction (FEV1 < 30% predicted) Mean FEV1 at diagnosis = 44% predicted (range 12–80%)
Schultz 1994 Cohort Canada 1980–1992	67	All patients who attended institutional follow-up post-aHSCT	Post: 1 year and with symptoms	10 with permanent obstructive lung disease Pre-aHSCT mean FEV1 = 106% predicted onset mean FEV1 = 51% predicted 3 had temporary obstruction with pre-aHSCT mean FEV1 = 103% predicted, mean FEV1 at onset of obstruction = 63% predicted Median time 7.5 months (range 3 to 55)
Walther 2020 Cohort Germany 2000–2017	14	Children with post-aHSCT BOS	Pre Post: at BOS diagnosis	FEV1 at BOS diagnosis = 58% predicted

parameters were similar in both groups [42]. In 2014, Srinivasan et al. [47] reported that lower pre-transplant FEF25–75% was associated with increased risk of subsequent pulmonary complications. Finally, a later study by Srinivasan et al. [48] found that T-cell depletion, reduced pre-transplantation FEV1, and cGVHD were associated with increased risk for pulmonary complications.

Frequency of post-transplant testing

The studies reviewed for this PICO question are listed in Table 3. We gathered data on whether PFT was performed post-transplant, and if so, the frequency of testing. We categorized studies into those that included at least one scheduled PFT measurement within the first 12 months post-transplant (regular surveillance) and those where PFT was not performed during this time frame, or

Table 4 Evidence profile of pre-transplant PFT data (PICO 1)

Quality assessment							No. of patients	Result	Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other				
Diagnostic yield: FEV1										
16	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	2200	All with normal FEV1 in 3 studies Range of prevalence of abnormal: 4–41%. Severe abnormalities: 0–13%	Moderate	Important
Diagnostic yield: FEV1/FVC										
13	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	909	All with normal FEV1/FVC in 2 studies Range of abnormalities: 5–20%	Moderate	Important
Diagnostic yield: FEF25-75%										
4	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	655	Range of abnormalities: 3–28%	Moderate	Important
Diagnostic yield: FVC										
10	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	1543	All with normal FVC in 2 studies Range of abnormalities: 10–31%	Moderate	Important
Diagnostic yield: DLCO										
10	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	914	All with normal DLCO in 1 study. Range of abnormalities: 3-100%	Moderate	Important

*Wide range of pre-transplant PFT abnormalities across studies

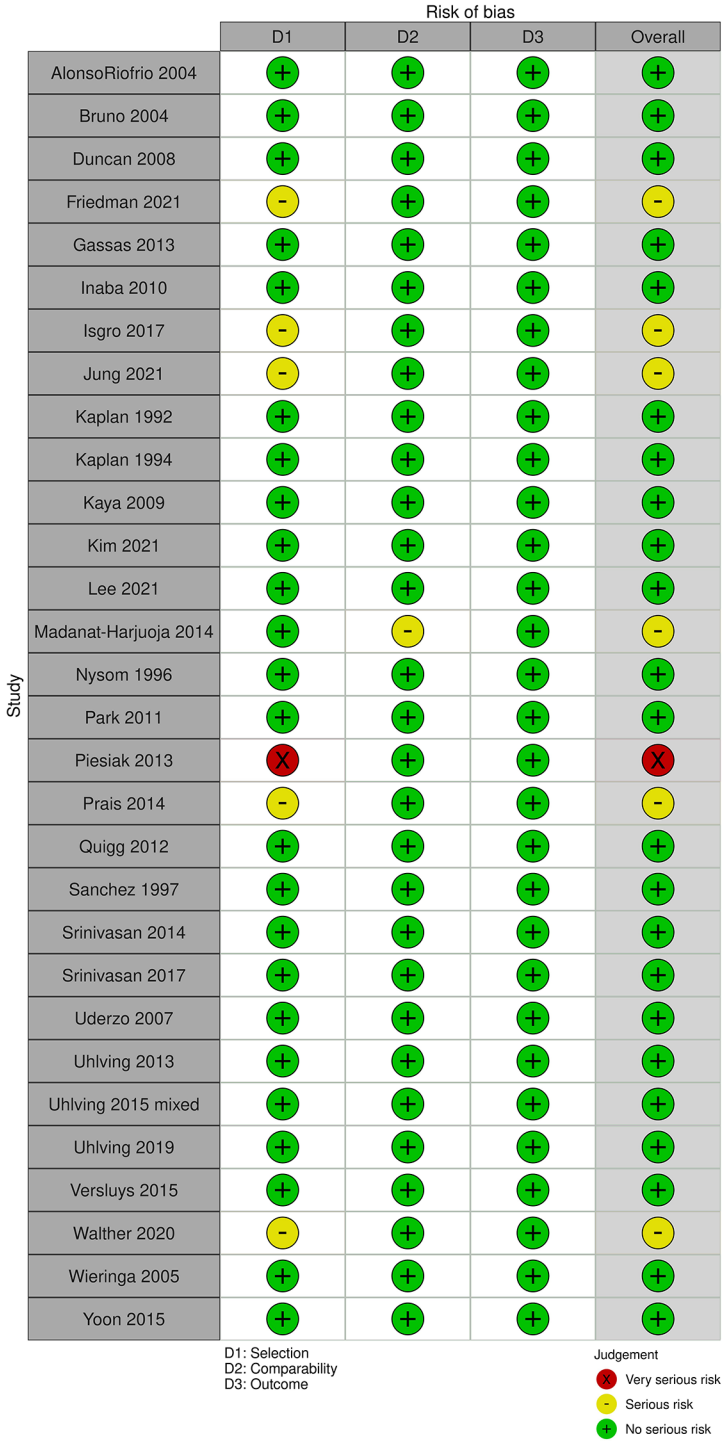

Fig. 3 Risk of bias assessment for the 30 studies used to address PICO 1

only in patients with symptoms. As with PICO question 1, we collected data on development of BOS or obstructive lung disease, and additional clinical outcomes including pulmonary complications, ICU admission, and mortality.

The aggregate findings for studies with regular surveillance versus those without are summarized in Table 5. Several studies for PICO 2 were determined to have serious risk of bias, and the data thus were deemed low to very low quality. A wide range of BOS severity was reported among studies, and some studies included only patients with BOS. Some studies only described obstructive airway disease without specifically addressing whether formal criteria for BOS were met. For this

Table 5 Evidence profile of post-transplant outcomes for patients undergoing post-transplant surveillance PFT versus patients who did not receive post-transplant surveillance PFT (PICO 2)

Quality assessment							No. of patients	Result	Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other				
Timing of BOS diagnosis										
21	Cohort studies	Serious*	None	None	None	None	1895	Surveillance: Most studies report median time to BOS diagnosis = 6–12 mos No surveillance: Median time to BOS diagnosis = 6–24 mos	Low	Critical
FEV1 decline at the time of diagnosis										
21	Cohort studies	Serious*	Serious†	None	None	None	1895	Surveillance: 38–84% predicted; 2 studies reported 4 patients being asymptomatic at BOS diagnosis No surveillance: 44–57% predicted and in one study FEV1 Z-score time of diagnosis − 3.62 (-4.77, -2.48)	Very Low	Critical

*Wide range of BOS severity among studies; some studies only included patients with BOS. Some studies only described obstructive airway disease without subclassifying them into BOS. Confounding variables such as conditioning regimens and pre-existing abnormal lung function tests were not controlled in most studies

†Wide range of FEV1 Z-score/percent predicted at diagnosis between studies

review, we treated obstructive lung disease as synonymous with BOS, understanding that this may result in some misclassification. Additionally, confounding variables such as conditioning regimens and pre-existing abnormal lung function tests were not controlled in most studies (Fig. 4 and Supplemental Table 2).

Post-transplant surveillance The year of transplant was before 2000 for all patients in nine studies, after 2000 for all patients in ten studies, while two studies included patients transplanted before and after 2000. Of the 21 studies, 11 reported regular post-aHSCT surveillance of PFT, and ten reported no regular surveillance. In nine of these 11, surveillance was performed with spirometry, measurement of static lung volumes, and DLCO. The other two studies used only spirometry. All studies reported FEV1 at a minimum. Of the nine studies reporting static lung volumes, five used body plethysmography [27, 37, 38, 48, 57], two used gas dilution [50, 55], and the authors did not state which technique was used in the remaining two [31, 56]. Among the 11 with regular surveillance, the frequency of testing ranged from one test in the first six months post-transplant in the oldest study [57] to every three months [27, 37]. All studies included pre-transplant PFT results for each patient, which were used as baseline values. Three studies reported regular PFT through 24 months post-aHSCT, and two performed PFT annually after the first 12 months. The most common schedule for PFT was pre-transplant, then 3, 6, 9–12, and 24 months post-transplant. Among patients both with and without BOS, a decline in lung function was observed between 3 and 9 months post-transplant; while some showed improvement between 6 and 24 months, others had continued decline for up to 10 years, sometimes without symptoms [28, 58, 60].

Identification of BOS Median time to identification of BOS in the 11 studies with regular surveillance was 6–12 months, with a range of 1–60 months. Mean percent predicted FEV1 was 38–84% at the time of diagnosis [34, 38]. Two studies reported a total of four patients who had not yet developed respiratory symptoms at the time of BOS diagnosis [31, 34]. Abnormalities in PFT results were associated with presence of cGVHD in other organ

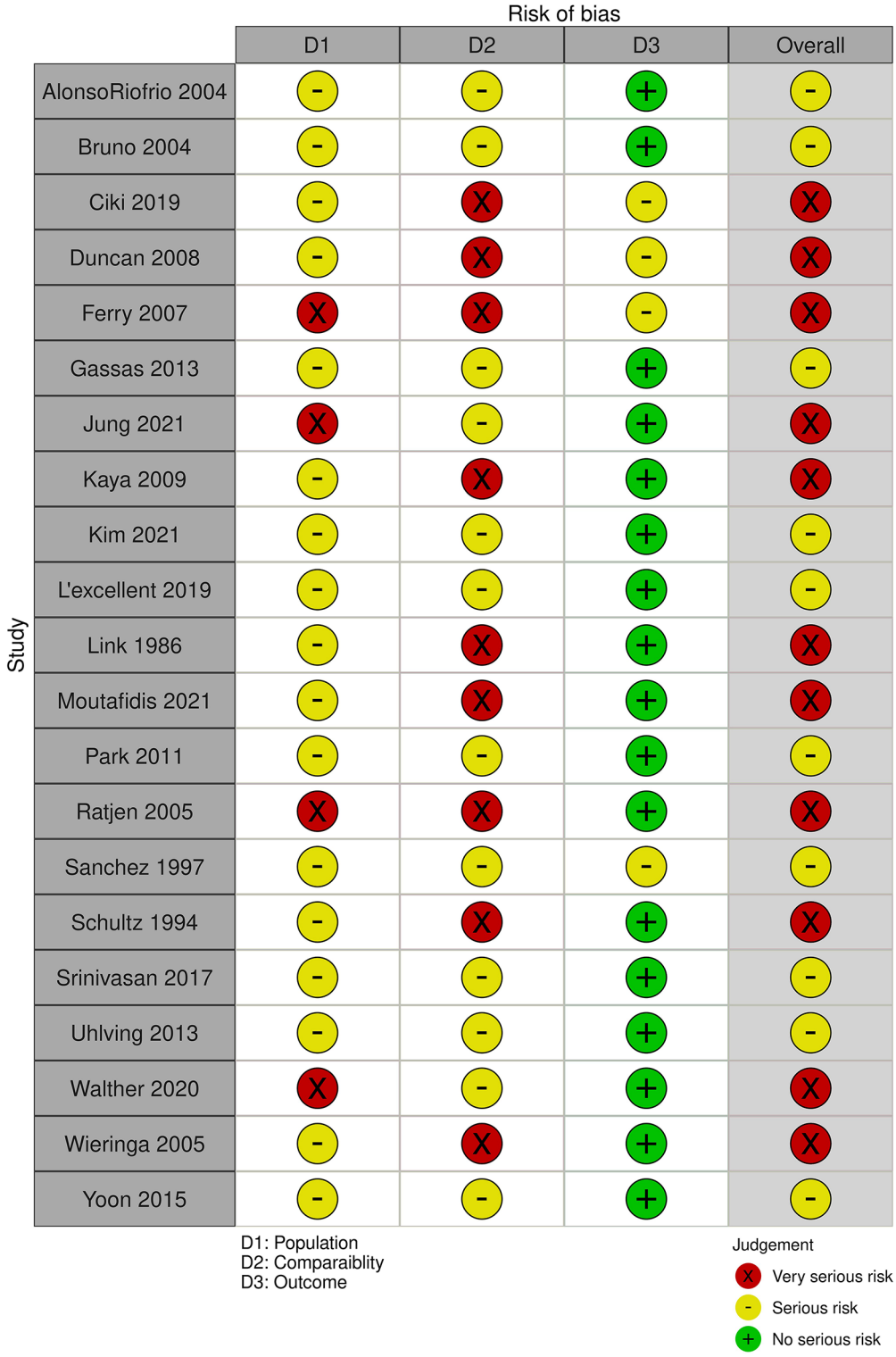

Fig. 4 Risk of bias assessment for the 21 studies used to address PICO 2

systems. One study that utilized spirometry, DLCO, and static lung volumes reported that DLCO and TLC were most associated with respiratory failure in the setting of BOS [37]. Jung et al. [34] reported that the extent of drop in FEV1 from pre-aHSCT to the time of diagnosis of BOS was not associated with mortality; however, the values of FEV1 were significantly lower at 6, 9, and 18 months after BOS diagnosis for patients who eventually

died or received lung transplantation. Ten studies did not utilize regular post-transplant PFT. In these, participants were tested at the time of symptom onset or some point thereafter. The median time to diagnosis of BOS was 6–24 months in these studies, with diagnosis occurring as far out as 107 months post-transplant. Mean percent predicted FEV1 at diagnosis was 44–57% [46, 63], with one study reporting a mean FEV1 z-score of -3.62 [61]. In a small cohort study of 20 children with obstructive lung disease after aHSCT, reduced mid-expiratory flow rate and elevated RV at the time of diagnosis of obstruction were associated with decreased response to immunosuppressive therapy [46].

Discussion

This systematic review was conducted to inform ATS guidelines on detection of BOS among pediatric aHSCT recipients. We have identified data suggesting that performing PFT pre-transplant, and at regular intervals in the first 1–2 years after transplant, may improve early identification of BOS. However, the data suggest some limitations of this approach, as BOS was often diagnosed at a point where significant pulmonary function impairment had already occurred.

The reviewed literature suggests that assessment of pre-aHSCT pulmonary function is useful for several reasons. The first is that abnormal pulmonary function is not uncommon prior to transplant. This is not surprising given that pediatric patients undergoing aHSCT are often at risk of pulmonary disease from a number of possible causes: sequelae of the primary disease process, airway or parenchymal injury from respiratory infections, as well as damage from prior chemo- or radiation therapy [1]. Identification of pulmonary function impairment pre-aHSCT allows for thorough evaluation and treatment of any identified pathology prior to transplant. Further, accurate determination of pre-aHSCT pulmonary function is vital for interpreting post-transplant results. If pulmonary function impairment is not identified pre-aHSCT, its discovery post-transplant will trigger concern for a transplant-related complication, resulting in a cascade of unnecessary investigation and treatment which could lead to patient harm. Lastly, there are data to suggest that pre-aHSCT pulmonary function is associated with post-transplant outcomes, pulmonary complications, need for mechanical ventilation, and mortality. If these findings are confirmed in future studies, then pre-aHSCT pulmonary function may allow for more personalized monitoring strategies for pulmonary complications, and more informed counseling of patients and families regarding the risks of aHSCT.

Post-transplant surveillance PFT also has value as it can lead to identification of BOS before overt symptoms develop, with a shorter median time to diagnosis than using symptom-triggered testing. Even with earlier detection of BOS, the level of pulmonary function impairment at the time of BOS diagnosis is significant. This is true even in studies which used the most frequent surveillance schedule of testing every three months, suggesting that BOS-related pulmonary function impairment occurs rapidly. While even more frequent testing may allow for detection of very early disease, studies are needed to assess the feasibility and efficacy of such an approach.

Because evidence suggests existing therapies may be more effective if given early in disease evolution [13, 15, 16], patients ideally would be diagnosed before significant impairment has occurred. Further evaluation [65] may be necessary when PFT abnormalities are detected, as it is possible that pulmonary function limitations in patients with cGVHD could reflect involvement of the chest wall fascia or respiratory muscles, or acute respiratory infection, rather than the airway injury typical of bronchiolitis obliterans [6]. Interventions or infections over the course of the transplant may also affect post-transplant PFT results. Some studies have reported cases of histology-proven bronchiolitis obliterans which do not meet criteria for BOS [29, 66], indicating that biopsy may still be considered in cases where suspicion is high regardless of PFT results. Development of pediatric-specific diagnostic criteria for BOS may offer the opportunity for improved detection in this population [2, 67].

When assessing the implementation of post-aHSCT surveillance testing, in addition to diagnostic yield, it is important to consider additional factors such as access (both to the test, and care that is needed for any abnormal results), cost, and experience of patients and families. In general, aHSCT is performed in highly-resourced settings, with previous work showing ample access to PFT as well as any subsequent tests and medical care that are needed following an abnormal result [21]. The costs of surveillance PFT are negligible compared to the aggregate costs of transplantation. Patients who receive aHSCT experience surveillance testing for other post-transplant complications, and PFT are non-invasive and generally acceptable.

The studies reviewed here have some limitations, many of which are related to cohort effects. Most studies included are single-center, and thus results may reflect practices specific to the study sites, which introduces heterogeneity and may limit generalizability. Inclusion criteria differ across studies, resulting in variability in several domains, including patient age, primary diagnosis, and type of transplant. We utilized a broad age range in our search strategy to be fully inclusive of the entire population that may be treated at pediatric transplant centers. Our inclusion of young adults may not reflect the population treated at all pediatric centers, limiting generalizability. The broad age range makes detection of associations

more difficult, as susceptibility of patients to BOS and/or ability of PFT to detect changes may vary by age. Because transplantation is a dynamic field, practices change over time, and patients in older studies may differ in important ways from those currently undergoing aHSCT. Samples sizes in many of the studies are relatively small, resulting in limited statistical power to detect subtle associations. The use of different reference datasets, and variable definitions of restrictive and obstructive disease, limits the comparability of studies. In studies without regular PFT surveillance, death from undiagnosed BOS may lead to survivorship bias in post-transplant PFT results. Lastly, limited data are available regarding whether surveillance PFT impacts important clinical outcomes such as ICU admission and mortality.

This review also highlights several areas where data are lacking. Prospective studies are needed to more fully characterize the relationships between pre-transplant PFT with later pulmonary complications and mortality. More data are required to determine optimal monitoring schedules and techniques to detect complications and optimize outcomes. Research is also needed on other modalities of testing more suited to younger patients, such as infant PFT, oscillometry, and multiple breath washout [68]. Large multicenter studies and registries would be ideal to address these and other critical questions to improve outcomes in this vulnerable population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05501-2.

Supplementary Material 1

Acknowledgements
Nil.

Author contributions
WAG – wrote manuscript. Reviewed and synthesized data. M TK, AVB, EC – performed abstract screening and extracted data from included paers. Reviewed and edited manuscript. EER – performed literature searchesSSh, SSr, CC, PCC, SD, SMD, JG, AS, CTT. SBG – Reviewed and synthesized data. Reviewed and edited manuscript. NPI – oversight of methodology and project overall. Reviewed and edited manuscript.

Funding
No funding was received for this review directly, but the clinic guideline development process was sponsored and funded by the American Thoracic Society.

Data availability
All data generated of analyzed during this study are included in this published article/ The authors can be contacted to provide any further detail on data extracted from the included papers.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Division of Pediatric Pulmonology, University of North Carolina School of Medicine, Chapel Hill, NC, USA
[2]Division of Pulmonary and Critical Care, Michigan State University College of Human Medicine and Spectrum Health, Grand Rapids, MI, USA
[3]Respiratory and Sleep Medicine, Royal Children's Hospital, Melbourne, Australia
[4]Respiratory Diseases, Murdoch Children's Research Institute, Melbourne, Australia
[5]Department of Paediatrics, University of Melbourne, Melbourne, Australia
[6]Department of Pediatrics, University of Tennessee College of Medicine and Le Bonheur Children's Hospital, Memphis, TN, USA
[7]St. Jude Children's Research Hospital, Memphis, TN, USA
[8]Woodruff Health Sciences Center Library, Emory University, Atlanta, GA, USA
[9]Laboratory of Asthma and Lung Inflammation, Critical Care Medicine and Pulmonary Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA
[10]Department of Internal Medicine, Saint Louis University, St Louis, MO, USA
[11]Pediatric Hematology and Immunology Department, Robert Debré Academic Hospital, GHU APHP Nord - Université de Paris, Paris, France
[12]Human Immunology, Pathophysiology and Immunotherapy, Institut de Recherche Saint-Louis, Paris, France
[13]Division of Pediatric Pulmonology, Allergy, and Sleep Medicine, Riley Hospital for Children, Indianapolis, IN, USA
[14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA
[15]Department of Pediatrics, Division of Pulmonary Medicine, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA
[16]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[17]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[18]Division of Pulmonary and Sleep Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[19]Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[20]Division of Pulmonary Medicine, Cincinnati Children's Hospital, Cincinnati, OH, USA
[21]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
[22]Division of Pulmonary Medicine, Masonic Children's Hospital, Minneapolis, MN, USA
[23]Division of Neonatology, Fetal and Neonatal Institute, Keck School of Medicine, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, USA

Received: 26 June 2024 / Accepted: 10 February 2025
Published online: 28 March 2025

References

1. Fitch T, Myers KC, Dewan M, Towe C, Dandoy C. Pulmonary complications after pediatric stem cell transplant. Front Oncol. 2021;11:755878.
2. Tamburro RF, Cooke KR, Davies SM, Goldfarb S, Hagood JS, Srinivasan A, et al. Pulmonary complications of pediatric hematopoietic cell transplantation. A national institutes of health workshop summary. Ann Am Thorac Soc. 2021;18(3):381–94.
3. Broglie L, Fretham C, Al-Seraihy A, George B, Kurtzberg J, Loren A, et al. Pulmonary complications in pediatric and adolescent patients following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transpl. 2019;25(10):2024–30.
4. Brissot E, Rialland F, Cahu X, Strullu M, Corradini N, Thomas C, et al. Improvement of overall survival after allogeneic hematopoietic stem cell

transplantation for children and adolescents: a three-decade experience of a single institution. Bone Marrow Transpl. 2016;51(2):267–72.
5. Holmqvist AS, Chen Y, Wu J, Battles K, Bhatia R, Francisco L, et al. Assessment of late mortality risk after allogeneic blood or marrow transplantation performed in childhood. JAMA Oncol. 2018;4(12):e182453.
6. Glanville AR, Benden C, Bergeron A, Cheng G-S, Gottlieb J, Lease ED et al. Bronchiolitis obliterans syndrome after lung or haematopoietic stem cell transplantation: current management and future directions. ERJ Open Res. 2022;8(3).
7. Chellapandian D, Lehrnbecher T, Phillips B, Fisher BT, Zaoutis TE, Steinbach WJ, et al. Bronchoalveolar lavage and lung biopsy in patients with cancer and hematopoietic stem-cell transplantation recipients: a systematic review and meta-analysis. J Clin Oncol. 2015;33(5):501–9.
8. Dieffenbach BV, Madenci AL, Murphy AJ, Weldon CB, Weil BR, Lehmann LE. Therapeutic impact and complications Associated with Surgical Lung Biopsy after Allogeneic hematopoietic stem cell transplantation in children. Biol Blood Marrow Transpl. 2019;25(11):2181–5.
9. Rossoff J, Locke M, Helenowski IB, Batra S, Katz BZ, Hijiya N. Cost analysis of bronchoalveolar lavage and respiratory tract biopsies in the diagnosis and management of suspected invasive fungal infection in children with cancer or who have undergone stem cell transplant. Pediatr Blood Cancer. 2019;66(5):e27598.
10. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and Staging Working Group report. Biol Blood Marrow Transpl. 2015;21(3):389–e4011.
11. Thangappan K, Morales DL, Winlaw D, Hayes D, Towe C, Schecter MG, et al. Risk factors for bronchiolitis obliterans syndrome in pediatric lung transplant recipients. J Heart Lung Transpl. 2021;40(4):S352.
12. Kwok W-C, Liang B-M, Lui MMS, Tam TCC, Sim JPY, Tse EWC, et al. Rapid versus gradual lung function decline in bronchiolitis obliterans syndrome after haematopoietic stem cell transplantation is associated with survival outcome. Respirology. 2019;24(5):459–66.
13. Cheng G-S, Storer B, Chien JW, Jagasia M, Hubbard JJ, Burns L, et al. Lung function trajectory in Bronchiolitis Obliterans Syndrome after Allogeneic hematopoietic cell transplant. Ann Am Thorac Soc. 2016;13(11):1932–9.
14. Williams KM. How I treat bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Blood. 2017;129(4):448–55.
15. DeFilipp Z, Kim HT, Yang Z, Noonan J, Blazar BR, Lee SJ, et al. Clinical response to belumosudil in bronchiolitis obliterans syndrome: a combined analysis from 2 prospective trials. Blood Adv. 2022;6(24):6263–70.
16. Williams KM, Cheng G-S, Pusic I, Jagasia M, Burns L, Ho VT, et al. Fluticasone, Azithromycin, and Montelukast Treatment for New-Onset Bronchiolitis Obliterans Syndrome after hematopoietic cell transplantation. Biol Blood Marrow Transpl. 2016;22(4):710–6.
17. Shenoy S, Gaziev J, Angelucci E, King A, Bhatia M, Smith A, et al. Late effects Screening guidelines after hematopoietic cell transplantation (HCT) for Hemoglobinopathy: Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late effects after Pediatric HCT. Biol Blood Marrow Transpl. 2018;24(7):1313–21.
18. Chow EJ, Anderson L, Baker KS, Bhatia S, Guilcher GMT, Huang JT, et al. Late effects Surveillance recommendations among survivors of Childhood hematopoietic cell transplantation: a children's Oncology Group Report. Biol Blood Marrow Transpl. 2016;22(5):782–95.
19. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Hematol Oncol Stem Cell Ther. 2012;5(1):1–30.
20. Rotz SJ, Bhatt NS, Hamilton BK, Duncan C, Aljurf M, Atsuta Y, et al. International Recommendations for Screening and Preventative Practices for Long-Term Survivors of Transplantation and Cellular Therapy: a 2023 Update. Transplantation Cell Therapy. 2024;30(4):349–85.
21. Shanthikumar S, Gower WA, Abts M, Liptzin DR, Fiorino EK, Stone A, et al. Pulmonary surveillance in pediatric hematopoietic stem cell transplant: a multinational multidisciplinary survey. Cancer Rep (Hoboken). 2022;5(5):e1501.
22. Shanthikumar S, Gower WA, Srinivasan S, Rayment JH, Robinson PD, Bracken J, et al. Detection of Bronchiolitis Obliterans Syndrome after Pediatric hematopoietic stem cell transplantation: an official American thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2024;210(3):262–80.
23. Higgins J, Thomas J, Chandler J, Cumptson M, Li T, Page M et al. Cochrane Handbook for Systematic Reviews of Interventions, version 6.3 (2022) [Internet]. 2022 [cited 2023 Dec 7]. Available from: https://training.cochrane.org/handbook/archive/v6.3
24. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–12.
25. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. 2012 [cited 2022 Dec 30]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
26. Canellas JVDS, Ritto FG, Rodolico A, Aguglia E, Fernandes GV, de O, Figueredo CM da. The international platform of registered systematic review and meta-analysis protocols (INPLASY) at 3 years: an analysis of 4,658 registered protocols on inplasy.com, platform features, and website statistics. Front Res Metr Anal. 2023;8:1135853.
27. Alonso Riofrío R, Villa Asensi JR, Sequeiros González A, Díaz Pérez MA, González Vicent M. Madero López L. [Obstructive lung disease after allogenic stem cell transplantation in children]. Pediatr (Barc). 2004;61(2):124–30.
28. Bruno B, Souillet G, Bertrand Y, Werck-Gallois MC, So Satta A, Bellon G. Effects of allogeneic bone marrow transplantation on pulmonary function in 80 children in a single paediatric centre. Bone Marrow Transpl. 2004;34(2):143–7.
29. Duncan CN, Buonanno MR, Barry EV, Myers K, Peritz D, Lehmann L. Bronchiolitis obliterans following pediatric allogeneic hematopoietic stem cell transplantation. Bone Marrow Transpl. 2008;41(11):971–5.
30. Friedman D, Dozor AJ, Milner J, D'Souza M, Talano J-A, Moore TB, et al. Stable to improved cardiac and pulmonary function in children with high-risk sickle cell disease following haploidentical stem cell transplantation. Bone Marrow Transpl. 2021;56(9):2221–30.
31. Gassas A, Craig-Barnes H, Dell S, Doyle J, Schechter T, Sung L, et al. Chest health surveillance utility in the early detection of bronchiolitis obliterans syndrome in children after allo-SCT. Bone Marrow Transpl. 2013;48(6):814–8.
32. Inaba H, Yang J, Pan J, Stokes DC, Krasin MJ, Srinivasan A, et al. Pulmonary dysfunction in survivors of childhood hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Cancer. 2010;116(8):2020–30.
33. Isgro' A, Marziali M, Paciaroni K, De Angelis G, Alfieri C, Ribersani M, et al. Spirometric evaluation of pulmonary function in Nigerian children underwent bone marrow transplantation for Sickle Cell Anemia. Mediterr J Hematol Infect Dis. 2017;9(1):e2017030.
34. Jung S, Yoon HM, Yoon J, Park M, Rhee ES, Kim H, et al. The association of lung function changes with outcomes in children with bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Pediatr Pulmonol. 2021;56(10):3332–41.
35. Kaplan EB, Wodell RA, Wilmott RW, Leifer B, Lesser ML, August CS. Chronic graft-versus-host disease and pulmonary function. Pediatr Pulmonol. 1992;14(3):141–8.
36. Kaplan EB, Wodell RA, Wilmott RW, Leifer B, Lesser ML, August CS. Late effects of bone marrow transplantation on pulmonary function in children. Bone Marrow Transpl. 1994;14(4):613–21.
37. Kaya Z, Weiner DJ, Yilmaz D, Rowan J, Goyal RK. Lung function, pulmonary complications, and mortality after allogeneic blood and marrow transplantation in children. Biol Blood Marrow Transpl. 2009;15(7):817–26.
38. Kim K, Lee HJ, Kim S, Lee JW, Yoon J-S, Chung NG, et al. Lung function predicts outcome in children with obstructive lung disease after hematopoietic stem cell transplantation. J Pediatr Hematol Oncol. 2021;43(1):e90–4.
39. Lee HJ, Kim K, Kim SK, Lee JW, Yoon J-S, Chung N-G, et al. Hb-adjusted DLCO with GLI reference predicts long-term survival after HSCT in children. Bone Marrow Transpl. 2021;56(8):1929–36.
40. Madanat-Harjuoja LM, Valjento S, Vettenranta K, Kajosaari M, Dyba T, Taskinen M. Pulmonary function following allogeneic stem cell transplantation in childhood: a retrospective cohort study of 51 patients. Pediatr Transpl. 2014;18(6):617–24.
41. Nysom K, Holm K, Hesse B, Ulrik CS, Jacobsen N, Bisgaard H, et al. Lung function after allogeneic bone marrow transplantation for leukaemia or lymphoma. Arch Dis Child. 1996;74(5):432–6.
42. Park M, Koh KN, Kim BE, Im HJ, Seo JJ. Clinical features of late onset non-infectious pulmonary complications following pediatric allogeneic hematopoietic stem cell transplantation. Clin Transpl. 2011;25(2):E168–76.
43. Piesiak P, Gorczynska E, Brzecka A, Kosacka M, Jankowska R. Pulmonary function impairment in patients undergoing allogeneic hematopoietic cell transplantation. Adv Exp Med Biol. 2013;755:143–8.
44. Prais D, Sinik MM, Stein J, Mei-Zahav M, Mussaffi H, Steuer G, et al. Effectiveness of long-term routine pulmonary function surveillance following

pediatric hematopoietic stem cell transplantation. Pediatr Pulmonol. 2014;49(11):1124–32.
45. Quigg TC, Kim Y-J, Goebel WS, Haut PR. Lung function before and after pediatric allogeneic hematopoietic stem cell transplantation: a predictive role for DLCOa/VA. J Pediatr Hematol Oncol. 2012;34(4):304–9.
46. Sánchez J, Torres A, Serrano J, Román J, Martín C, Pérula L, et al. Long-term follow-up of immunosuppressive treatment for obstructive airways disease after allogeneic bone marrow transplantation. Bone Marrow Transpl. 1997;20(5):403–8.
47. Srinivasan A, Srinivasan S, Sunthankar S, Sunkara A, Kang G, Stokes DC, et al. Pre-hematopoietic stem cell transplant lung function and pulmonary complications in children. Ann Am Thorac Soc. 2014;11(10):1576–85.
48. Srinivasan A, Sunkara A, Mitchell W, Sunthankar S, Kang G, Stokes DC, et al. Recovery of pulmonary function after Allogeneic Hematopoietic Cell Transplantation in Children Is Associated with Improved Survival. Biol Blood Marrow Transpl. 2017;23(12):2102–9.
49. Uderzo C, Pillon M, Corti P, Tridello G, Tana F, Zintl F, et al. Impact of cumulative anthracycline dose, preparative regimen and chronic graft-versus-host disease on pulmonary and cardiac function in children 5 years after allogeneic hematopoietic stem cell transplantation: a prospective evaluation on behalf of the EBMT Pediatric Diseases and Late effects Working parties. Bone Marrow Transpl. 2007;39(11):667–75.
50. Uhlving HH, Bang CL, Christensen IJ, Buchvald F, Nielsen KG, Heilmann CJ, et al. Lung function after allogeneic hematopoietic stem cell transplantation in children: a longitudinal study in a population-based cohort. Biol Blood Marrow Transpl. 2013;19(9):1348–54.
51. Uhlving HH, Mathiesen S, Buchvald F, Green K, Heilmann C, Gustafsson P, et al. Small airways dysfunction in long-term survivors of pediatric stem cell transplantation. Pediatr Pulmonol. 2015;50(7):704–12.
52. Uhlving HH, Skov L, Buchvald F, Heilmann C, Grell K, Ifversen M, et al. Lung clearance index for early detection of pulmonary complications after allo-HSCT in children. Pediatr Pulmonol. 2019;54(7):1029–38.
53. Versluys AB, van der Ent K, Boelens JJ, Wolfs T, de Jong P, Bierings MB. High diagnostic yield of dedicated pulmonary screening before hematopoietic cell transplantation in children. Biol Blood Marrow Transpl. 2015;21(9):1622–6.
54. Walther S, Rettinger E, Maurer HM, Pommerening H, Jarisch A, Sörensen J, et al. Long-term pulmonary function testing in pediatric bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Pediatr Pulmonol. 2020;55(7):1725–35.
55. Wieringa J, van Kralingen KW, Sont JK, Bresters D. Pulmonary function impairment in children following hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2005;45(3):318–23.
56. Yoon J-S, Chun YH, Lee JW, Chung NG, Cho B. Value of screening spirometry for early diagnosis of bronchiolitis obliterans syndrome in children after allogeneic hematopoietic stem cell transplantation. J Pediatr Hematol Oncol. 2015;37(8):e462–7.
57. Link H, Reinhard U, Blaurock M, Ostendorf P. Lung function changes after allogenic bone marrow transplantation. Thorax. 1986;41(7):508–12.
58. Çıkı K, Doğru D, Kuşkonmaz B, Emiralioğlu N, Yalçın E, Özçelik U, et al. Pulmonary complications following hematopoietic stem cell transplantation in children. Turk J Pediatr. 2019;61(1):59–60.
59. Ferry C, Gemayel G, Rocha V, Labopin M, Esperou H, Robin M, et al. Long-term outcomes after allogeneic stem cell transplantation for children with hematological malignancies. Bone Marrow Transpl. 2007;40(3):219–24.
60. L'excellent S, Yakouben K, Delclaux C, Dalle J-H, Houdouin V. Lung evaluation in 10 year survivors of pediatric allogeneic hematopoietic stem cell transplantation. Eur J Pediatr. 2019;178(12):1833–9.
61. Moutafidis D, Gavra M, Golfinopoulos S, Oikonomopoulou C, Kitra V, Woods JC, et al. Lung hyperinflation quantitated by chest CT in children with bronchiolitis obliterans syndrome following allogeneic hematopoietic cell transplantation. Clin Imaging. 2021;75:97–104.
62. Ratjen F, Rjabko O, Kremens B. High-dose corticosteroid therapy for bronchiolitis obliterans after bone marrow transplantation in children. Bone Marrow Transpl. 2005;36(2):135–8.
63. Schultz KR, Green GJ, Wensley D, Sargent MA, Magee JF, Spinelli JJ, et al. Obstructive lung disease in children after allogeneic bone marrow transplantation. Blood. 1994;84(9):3212–20.
64. Gassas A, Craig-Barnes H, Dell SD, Cox P, Schechter T, Doyle J, et al. Severe lung injury and lung biopsy in children post-hematopoietic stem cell transplantation: the differences between allogeneic and autologous transplantation. Pediatr Transpl. 2013;17(3):278–84.
65. Walker H, Shanthikumar S, Cole T, Neeland M, Hanna D, Haeusler GM. Novel approaches to the prediction and diagnosis of pulmonary complications in the paediatric haematopoietic stem cell transplant patient. Curr Opin Infect Dis. 2022;35(6):493–9.
66. Uhlving HH, Andersen CB, Christensen IJ, Gormsen M, Pedersen KD, Buchvald F, et al. Biopsy-verified bronchiolitis obliterans and other noninfectious lung pathologies after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transpl. 2015;21(3):531–8.
67. Shanthikumar S, Gower WA, Cooke KR, Bergeron A, Schultz KR, Barochia A, et al. Diagnosis of post-hematopoietic stem cell transplantation bronchiolitis Obliterans Syndrome in Children: time for a Rethink? Transplantation Cell Therapy. 2024;30(8):760–9.
68. Sonneveld N, Rayment JH, Usemann J, Nielsen KG, Robinson PD. Multiple breath washout and oscillometry after allogenic HSCT: a scoping review. Eur Respir Rev. 2023;32(169).

Publisher's note