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ORIGINAL ARTICLE

Pulmonary complications post allogeneic haematopoietic stem cell transplant in children

Hannah Walker[1,2,3], Joanne Abbotsford[4], Gabrielle M Haeusler[2,3,5,6,7,8], Daniel Yeoh[3,4], Shanti Ramachandran[9,10], Michelle Ng[9], Jonathan Holzmann[9], Shivanthan Shanthikumar[2,3,11], Heather Weerdenburg[1,2,3], Diane Hanna[1,2,3,8], Melanie R Neeland[2,3,a] & Theresa Cole[1,2,3,12,a]

[1]Children's Cancer Centre, Royal Children's Hospital, Parkville, VIC, Australia
[2]Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia
[3]Murdoch Children's Research Institute, Parkville, VIC, Australia
[4]Department of Infectious diseases, Perth Children's Hospital, Nedlands, WA, Australia
[5]Infection Diseases Unit, Department of General Medicine, Royal Children's Hospital, Parkville, VIC, Australia
[6]Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia
[7]NHMRC National Centre for Infections in Cancer, Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, VIC, Australia
[8]The Paediatric Integrated Cancer Service, Parkville, VIC, Australia
[9]Department of Clinical Haematology, Oncology and Bone Marrow Transplantation, Perth Children's Hospital, Nedlands, WA, Australia
[10]Division of Paediatrics, University of Western Australia Medical School, Perth, WA, Australia
[11]Respiratory and Sleep Medicine, Royal Children's Hospital, Parkville, VIC, Australia
[12]Allergy and Immunology, Royal Children's Hospital, Parkville, VIC, Australia

Correspondence
H Walker, Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Rd, Parkville, VIC 3052, Australia.
E-mail: hannah.walker@rch.org.au

[a]Equal contributors.

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Abstract

Objectives. Haematopoietic stem cell transplant (HCT) is a cellular therapy that, whilst curative for a child's underlying disease, carries significant risk of mortality, including because of pulmonary complications. The aims of this study were to describe the burden of pulmonary complications post-HCT in a cohort of Australian children and identify risk factors for the development of these complications. **Methods.** Patients were identified from the HCT databases at two paediatric transplant centres in Australia. Medical records were reviewed, and demographics, HCT characteristics and pulmonary complications documented. Relative risk ratio was used to identify risk factors for developing pulmonary complications prior to first transplant episode, and survival analysis performed to determine hazard ratio. **Results.** In total, 243 children underwent transplant during the study period, and pulmonary complications occurred in 48% (117/243) of children. Infectious complications were more common (55%) than non-infective complications (18%) and 26% of patients developed both. Risk factors for the development of pulmonary complications included the following: diagnoses of MPAL (RR 2.16, $P = 0.02$), matched unrelated donor (RR1.34, $P = 0.03$), peripheral blood (RR 1.36, $P = 0.028$) or cord blood (RR 1.73, $P = 0.012$) as the stem cell source and pre-existing lung disease (RR1.72, $P < 0.0001$). Children with a post-HCT lung complication had a significantly increased risk of mortality compared with those who did not (HR 3.9, $P < 0.0001$). **Conclusion.** This study

demonstrates pulmonary complications continue to occur frequently in children post-HCT and contribute significantly to mortality. Highlighting the need for improved strategies to identify patients at risk pre-transplant and enhanced treatments for those who develop lung disease.

Keywords: haematopoietic stem cell transplant, infection, paediatric, pulmonary complications

INTRODUCTION

Allogeneic haematopoietic stem cell transplant (HCT) is a cellular therapy used to treat children with a range of life-threatening conditions, including inborn errors of immunity, metabolic storage disorders, haemoglobinopathies and haematological malignancies. Whilst the goal of HCT is to cure the child's underlying condition, it has a range of potentially serious complications, including pulmonary complications.[1] Pulmonary complications following HCT contribute a high proportion of non-relapse mortality.[2–7] Because of advances in supportive care, antimicrobial prophylaxis and treatments, outcomes from infectious pulmonary complications have improved in recent years.[8] In comparison, non-infectious pulmonary complications including bronchiolitis obliterans (BO), idiopathic pneumonia syndrome (IPS) and engraftment syndrome[1,5] have limited methods for early detection and targeted therapy, with outcomes remaining poor.[9] Large, primarily adult, studies have identified a range of risk factors for the development of post-HCT pulmonary complications. These include chemotherapy agents such as busulfan, cyclophosphamide and methotrexate, which are frequently used as part of the patients conditioning regimen.[8,10,11] Other risk factors include total body irradiation (TBI), pre-existing lung disease,[8] HLA mismatch, graft vs host disease (GvHD) and clinical indication for HCT.[2,8,12]

There are limited published data on the specific types of pulmonary complications in children post-HCT and their long-term outcomes.[8] Research has previously focussed on the experience in adults post-transplant or combined adult and paediatric cohorts. Rates of pulmonary complications post-HCT in adults are reported to occur between 30% and 40%.[13,14] Published data in paediatric patients, collected between 1996 and 2015,[2–4,7] reported incidence of pulmonary complications (36–74%) and associated mortality (25–65%) and have varied widely. Importantly, there have been several significant changes in practice since these data were generated, including increased use of immunotherapy prior to HCT, changes in chemotherapy conditioning regimens for acute lymphoblastic leukaemia (ALL) with improved outcomes for a TBI backbone (FORUM trial),[15] increased use of reduced intensity conditioning (RIC) regimens and an increase in the use of haploidentical donors.[16] There have also been advancements in supportive care post-HCT, including pre-emptive screening and treatment for viral reactivation and increased use of steroid sparing agents for GVHD post-HCT. These factors, which have changed the landscape of paediatric allogeneic transplant in the last 10 years, may have impacted the characteristics and impact of pulmonary complications post-HCT. Another key limitation of previous studies is that they have combined outcomes for both autologous and allogeneic transplants, which are likely to have different risk profiles for post-HCT complications. Additionally, many of these studies were conducted in single centres and may not consider variability between transplant centres.

The primary aim of this study was to describe the characteristics and impact of pulmonary complications post-HCT in a multicentre paediatric cohort undergoing allogeneic HCT, reflecting current practice. The secondary aims of this study were to identify both protective and risk factors for the development of pulmonary complications and to identify factors predicting poor outcome following pulmonary complications.

RESULTS

Cohort demographics and aetiology of pulmonary complications

The study identified 268 episodes of paediatric allogeneic HCT in 243 individual patients (Figure 1a). The median follow-up was 32.5 months post HSCT. Pulmonary complications

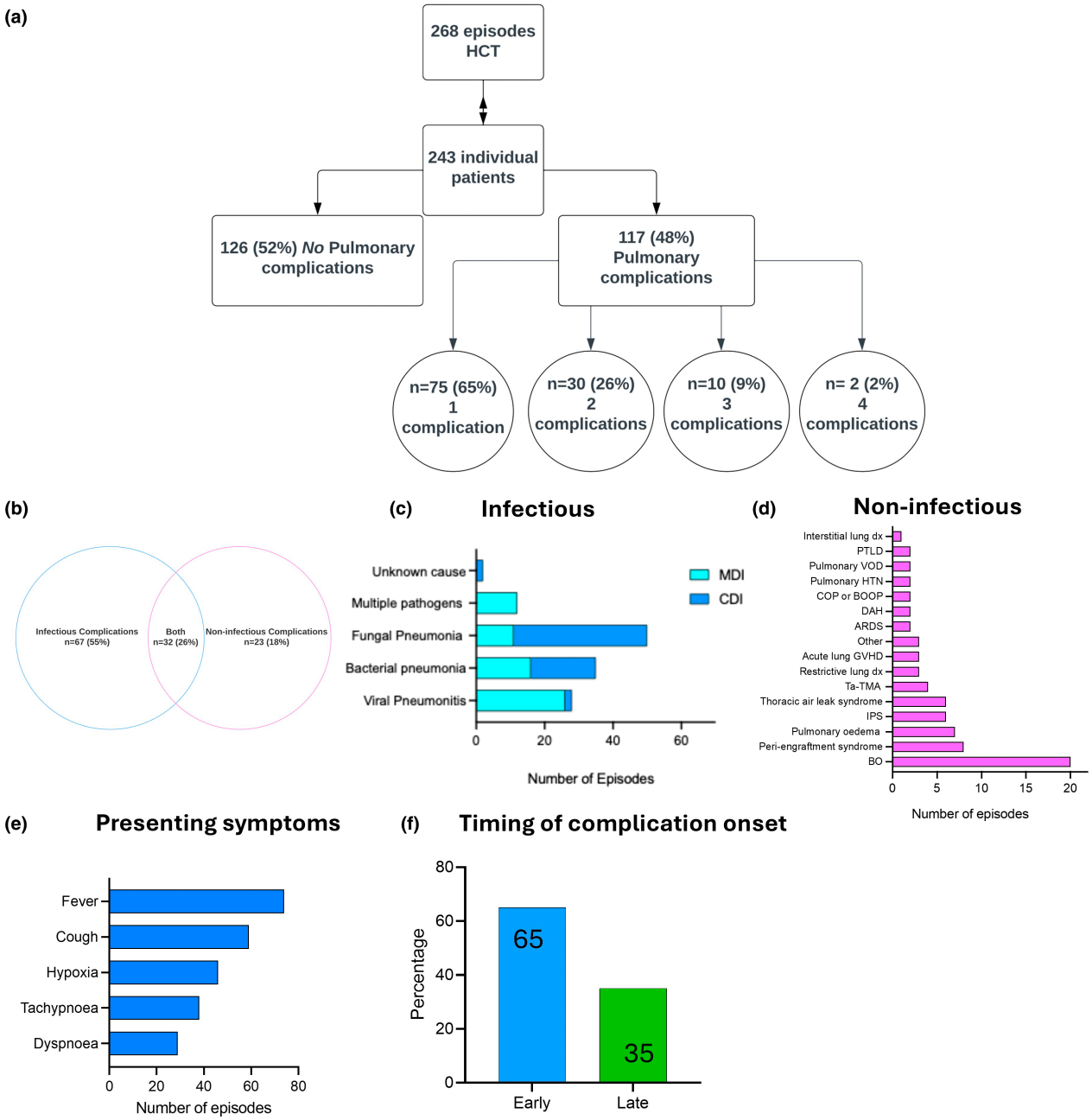

Figure 1. Cohort demographics and aetiology of pulmonary complications **(a)** Flow chart depicting patient and transplant episode and rates of development of pulmonary complications **(b)** Aetiology of lung complications shows infectious complications were the most common cause **(c)** Infectious complications aetiology including MDI and CDI: shows high proportion of possible fungal infection, viral pneumonitis and bacterial pneumonia. **(d)** Types of non-infectious pulmonary complications: shows bronchiolitis obliterans (BO) and peri-engraftment syndrome were the most common causes. **(e)** Presenting symptoms of pulmonary complication: shows non-specific symptom of fever was the most common. **(f)** Timing of complication onset: demonstrating most complications started early post-transplant in the first 100 days.

occurred in 48% (117/243) of patients, and within this group, 35% (42/117) of patients developed more than one pulmonary complication (Figure 1a). Demographics of the cohort including age and indication for *first transplant episode* (pulmonary complication; $n = 115$ patients) are shown in Table 1. The most common indications for HCT were malignancies, B-cell acute

Table 1. Demographics and risk of developing pulmonary complication *post first* HCT episode

Characteristic	Pulmonary complication (*n* = 115)	No pulmonary complication (*n* = 128)
Age in years at HCT Day 0		
Median (IQR)	6.8 (2.3–13.8)	7.05 (3.67–11.6)
Age < 1 year (*n*, %)	19 (16.5)	15 (11.8)
Age 1.1–4 years	18 (15.6)	24 (18.9)
Age 4.1–12	42 (26.5)	61 (47.6)
Age > 12.1 years	37 (32.1)	27 (21.2)
Male, *n* (%)	73 (51.4)	69 (48.59)
Diagnosis, *n* (%)		
Malignant	75 (48.4)	80 (51.6)
Non-malignant	54 (50.4)	53 (49.5)
Specific diagnoses		
B-ALL	19 (16.5)	25 (19.5)
AML	21 (18.2)	25 (19.5)
Mixed phenotype ALL	5 (4.3)	0
Primary immunodeficiency (any)	28 (23.9)	23 (17.9)
Haemoglobinopathies	4 (3.5)	3 (2.3)
Metabolic disorder	8 (7)	3 (2.3)
Aplastic anaemia	3 (2.6)	13 (10.1)
Stem cell source, *n* (%)		
Bone marrow	34 (29)	67 (52)
Peripheral blood stem cells	68 (59)	57 (44)
Cord blood	14 (12)	4 (0.03)
Donor type		
Haploidentical	28 (24)	30 (23)
Matched unrelated	58 (50)	47 (37)
Matched sibling	29 (25)	51 (40)
Conditioning regimen		
Myeloablative	85 (73)	80 (62.5)
Conditioning details		
BU/FLU	42 (36.5)	50 (39)
TREO/FLU	32 (27.8)	25 (19.5)
CY	17 (14.8)	32 (25)
MEL	8 (7)	13 (10.1)
TBI any, *n* (%)	23 (20)	30 (23.4)
Serotherapy		
Alemtuzumab	18 (15.6)	20 (15.6)
ATG	61 (53)	54 (47)
GVHD prophylaxis		
MTX + CNI	25 (21.7)	29 (12)
MMF + CNI	50 (43.5)	47 (36.7)
CNI only	31 (27)	37 (29)
Methylprednisolone	4 (3.5)	0
TCR α/β depletion	17/68 (25)	17/57 (29)
Required a second HCT	18 (15)	11 (8.6)
Previous B-cell immunotherapy[a]	14 (12.2)	20 (15.6)
Chemotherapy pre-HCT	64 (55.7)	80 (62.5)
Radiation (any including TBI)	3 (2.6)	10 (7.8)
Abnormal chest CT pre-HCT[b]	72 (69.2)	59 (45)
Infection history pre-HCT		
Active lung infection 30 days pre-HCT	21 (18.2)	13 (10.2)
Lung disease history pre-HCT[c]	63 (54.7)	36 (28.2)
Pneumonia	31 (27)	17 (35.4)
Bronchiectasis	6 (5.2)	1 (0.8)
Mechanical ventilation	10 (8.7)	5 (3.9)

AML, Acute Myeloid Leukaemia; ATG, Anti-thymocyte globulin; B-ALL, B-Cell Acute Lymphoblastic Leukaemia; BU/FLU, Busulfan/Fludarabine; CNI, Calcineurin inhibitor; CY, Cyclophosphamide; IQR, Interquartile range; MEL; Melphalan; MMF, Mycophenylate; MTX, Methotrexate; TBI, Total Body Irradiation; TCR α/β, T-Cell receptor alpha/beta; TREO/FLU, Treosulfan/Fludarabine.

[a]Previous Immunotherapy included blinatumomab, inotuzumab and CAR-T therapy.

[b]Abnormal CT included nodules, pleural effusion and consolidation.

[c]Lung dx included any of the following: asthma, pneumonia, bronchiectasis, ARDS, ACS, and mechanical ventilation.

lymphoblastic leukaemia (B-ALL) [18% (44/243)] and acute myeloid leukaemia (AML) [19% (46/243)]. Transplant occurred at a median age of 7 years (IQR 3.1–12.75).

The aetiology of the pulmonary complications is detailed in Figure 1b–d. There were 99 infective diagnoses and 55 non-infective pulmonary complication episodes identified in patients post-HCT (follow-up included if patients developed a lung complication post second transplant if captured in the study period). Many patients received more than one diagnoses in both categories, reflected in the total diagnoses exceeding the number of patients. In patients who developed an infective complication, there were 63 episodes of MDI and 37 episodes of CDI. The contribution of types of MDI is shown in Figure 1c; viral pneumonitis was the most common in 11% (26/243) followed by bacterial pneumonia, which is common in 7% (16/243). MDI related to fungal infection included both probable and proven fungal infection in 4.5% (11/243). Infection with multiple organisms, most commonly viral and fungal infection, was

reported in 5% (12/243). The most common respiratory viruses detected on PCR were cytomegalovirus (CMV) [5% (13/243)], rhinovirus [4.5% (11/243)], adenovirus [3% (8/243)] and human parainfluenza types 1–3 [4% (10/243)] (Supplementary table 2). Organisms identified on BAL sampling are shown in Supplementary table 2 and included two episodes of *Pseudomonas* spp.

Episodes of clinically defined respiratory tract infection are shown in Supplementary table 3; the most commonly occurring were IFI in 16% (39/243); bacterial pneumonia in 8% (19/243) of episodes; and viral pneumonitis in 1% (2/243). Of the CDI related to possible fungal disease, 64% (25/39) were also attributed to another microbiological, clinical or non-infectious pulmonary cause. This reflects the clinical strategy to treat pre-emptively for possible IFI in patients post-HCT with suspicion of a pulmonary complication whilst awaiting further diagnostics. There was one episode of sepsis, which was presumed related to a pulmonary source but was culture negative, and one episode of laryngotracheobronchitis, which was also reported as a CDI.

Overall, there were 54 episodes of pulmonary IFI [22%, (54/243)], the majority were classified as possible fungal infection only [72%, (39/54)]. There was low frequency of both probable 13% (7/54) and proven pulmonary 7% IFI (4/54). Of the proven and probable, three were attributed to *Aspergillus* spp., two because of *candida* spp. and two because of PJP. Both patients with episodes of PJP were identified to have poor compliance with the use of PJP prophylaxis medications (trimethoprim and sulfamethoxazole).

The non-infective diagnoses are shown in Figure 1d; the most commonly occurring were BO [8%, (20/243)], engraftment or peri-engraftment syndrome [3%, (8/243)], idiopathic pneumonia syndrome (IPS) [2%, (6/243)] and thoracic air leak syndrome [2%, (6/243)]. Of note, some individual patients in this group also developed more than one non-infective diagnoses, including one patient developed pulmonary haemorrhage, which led to progressive pulmonary fibrosis and thoracic air leak syndrome.

Figure 1e shows the most common presenting symptoms and signs at the onset of the pulmonary complication episode ($n = 125$). These included fever [59%, (74/125)], cough [47%, (59/125)] and hypoxia [37%, (46/125)]. Pulmonary complication episodes occurred initially more frequently in the first 100 days of HCT ($n = 81$, 65%) compared with after 100 days ($n = 44$, 35%) (Figure 1f). The most common initial imaging performed was a chest x-ray [72%, (90/125)], followed by CT scan [57%, (71/125)]. Of those who had a CXR as an initial investigation, 35% (32/90) had a subsequent CT chest. Bronchoalveolar lavage was performed in 45% (56/125) and lung biopsy in only 6% (8/125).

Infection prophylaxis most prescribed for all patients at the time of hospital admission was the combination of trimethoprim and sulfamethoxazole for PJP [89%, (216/243)], acyclovir for viral prophylaxis [95%, (232/243)] and fluconazole [72%, (174/243)] or micafungin [16%, (39/243%)] for fungal prophylaxis. Data on initial treatment were also collected in the first 24 h post onset of pulmonary complication symptoms. A large proportion of patients were already receiving antibiotics at the time of presentation [43%, (54/125)], with piperacillin–tazobactam the most common, in keeping with empiric treatment of febrile neutropenia in this group. Piperacillin–tazobactam was also the most frequently prescribed initial antibiotic for treatment in this group [22%, (28/125)]. Liposomal amphotericin [19%, (24/125)] was the most common initial antifungal treatment prescribed. Treatment for specific non-infective pulmonary complications is detailed in Supplementary table 4, with corticosteroids (both inhaled and/or systemic) the most prescribed agent [27%, (34/125)].

Mortality associated with the development of pulmonary complications and implications of disease severity

Survival analysis revealed a 3.9-fold increase in mortality in patients who developed a pulmonary complication compared with those who did not (Figure 2a, $P < 0.0001$). Within the cohort who developed pulmonary complications, admission to a paediatric intensive care unit (PICU) was associated with an 11.4-fold increase in mortality compared with no PICU admission ($P < 0.0001$, Figure 2b). The requirement for ventilation related to the pulmonary complication was associated with a 70-fold increase in mortality compared with no requirement for ventilation ($P < 0.0001$, Figure 2c).

Supplementary table 5 details aspects of disease severity in the total group and those who developed pulmonary complications. Among

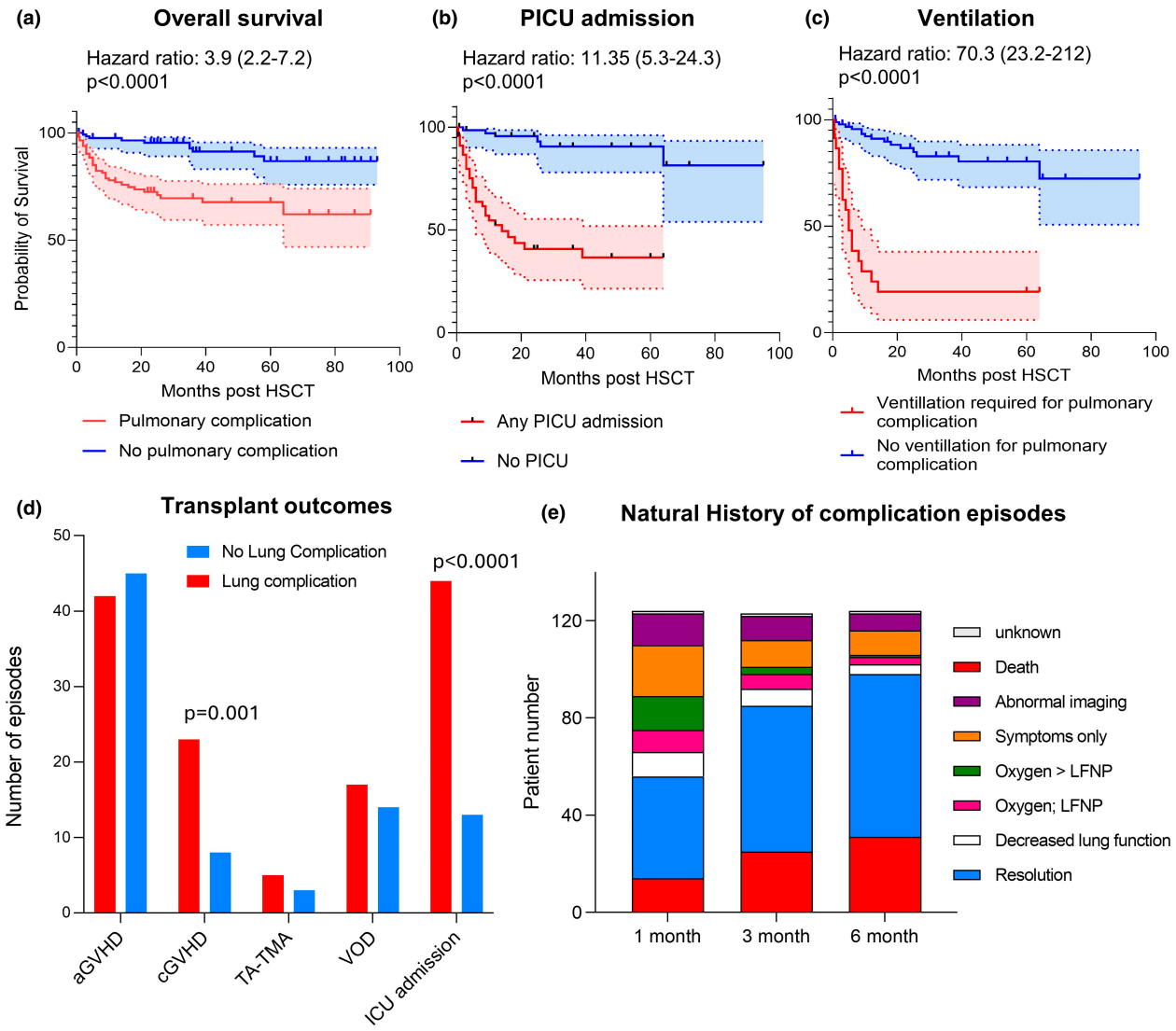

Figure 2. Mortality in children who developed pulmonary complications and general transplant outcomes. **(a)** Worse overall survival of children who developed a pulmonary complication post-HCT: survival analyses performed using Kaplan–Meyer method, HR 3.9, $P < 0.0001$. **(b)** Children who required PICU admission for pulmonary complication; inferior survival, HR 11.35 $P < 0.0001$. **(c)** Ventilation in children who developed a pulmonary complication had the poorest survival: Compared to children with a lung complication who did not require ventilation, HR 70.3 $P < 0.0001$. **(d)** General transplant outcomes in children who developed a pulmonary complication: increased rates of cGVHD $P = 0.001$ and any ICU admission $P < 0.0001$. **(e)** Natural history of children who developed a pulmonary complication: The majority of children have complete resolution of disease without residual lung imaging changes or symptoms at 6 months post disease onset.

those with pulmonary complications, 26% (30/115) required admission to a paediatric intensive care unit, and 19% (22/115) developed chronic pulmonary disease. Mortality associated with pulmonary disease was 6% (14/243), comprising the majority of non-relapse mortality (NRM). This was higher than the number of patients whose mortality was attributed to relapse after the *first* transplant in the total cohort (4.5%, 11/243). In the cohort requiring a *second* transplant ($n = 29$), mortality because of disease recurrence was more common [28%, (8/29)] than death from pulmonary disease (14%, 4/29).

A comparison of general transplant outcomes between the group who developed pulmonary complications and those who did not showed

higher rates of chronic graft versus host disease (cGVHD) [20%, (23/115) vs 6%, (8/128), $P = 0.0018$] and admission to PICU for any reason [38%, (44/115) vs 10%, (13/128), $P < 0.0001$] in those who developed pulmonary disease (Figure 2d). There were no statistical differences in rates of acute graft versus host disease (aGVHD) [37%, (42/115) vs 36%, (45/125), $P = 0.89$], VOD [15%, (17/115) vs 11%, (14/128), $P = 0.37$] or transplant-associated thrombotic microangiopathy [4%, (5/115) vs 2%, (3/128), $P = 0.48$] between the groups (Supplementary table 6).

The natural history of patients who developed a pulmonary complication episode is shown in the response to therapy at 1, 3 and 6 months post presentation of the pulmonary complication (Figure 2e). Overall, 58% (67/115) had complete resolution by 6 months, 3% (4/115) had ongoing oxygen requirement, and 26% (30/115) had died.

Risk factors for the development of post-HCT pulmonary complications

We identified several risk factors associated with the development of post-HCT pulmonary complications (Figure 3 and Table 1). This included diagnoses of mixed phenotype ALL (RR 2.16, $P = 0.02$), matched unrelated donor (RR 1.34, $P = 0.03$), peripheral blood (RR 1.36, $P = 0.028$) or cord blood (RR 1.73, $P = 0.012$) as the stem cell source, and pre-existing pulmonary disease (RR 1.72, $P < 0.0001$) including abnormal CT pre-HCT (RR 1.42, $P = 0.02$). The following protective factors were associated with a decreased risk of developing post-HCT pulmonary disease: a diagnoses of aplastic anaemia (RR 0.38, $P = 0.02$), bone marrow as the stem cell source (RR 0.59, $P = 0.0003$) and having a matched sibling as the available donor (RR 0.68, $P = 0.02$). There was no statistically significant difference between patients who received a particular chemotherapy agent or TBI as part of the conditioning regimen (Figure 3).

Non-relapse mortality because of pulmonary disease

The detail of 18 patients who died because of a pulmonary complication, post first or second HCT, is included in Supplementary table 7. The following themes were identified in this high-risk group including the following: higher incidence of MMRD 54.5% (12/22) and PBSC 77.3% (17/22) compared with the whole cohort. Patients were also more likely to present at the time of complication with hypoxia 75% (15/20) compared with cough 30% (6/20) and fever 40% (8/20) in the cohort who died. As Supplementary table 7 illustrates patients were also more likely to have multiple aetiological factors, both infective and non-infective in 77%, (14/18) compared with the whole cohort in 26% (32). CMV disease was also a frequent contributor to aetiology of lung disease in these cases of TRM in 44% (8/18) and the most commonly implicated pathogen. There was no statistical difference between TRM in the patients who had early onset compared with late onset of the pulmonary complication $P = 0.784$, RR 0.8 (CI 0.36–1.89).

DISCUSSION

This study highlights that pulmonary complications occurred frequently post allogeneic HCT and were associated with high NRM in children. The survival data in this group clearly show the negative impact of pulmonary complications on survival of children post-HCT. Particularly, that death related to pulmonary complications occurred more frequently than malignant disease relapse in the setting of first transplant. The interesting dichotomy of this study showed that survivors post an episode of pulmonary complication were more likely to have minimal morbidity and recover completely within 6 months. Alternatively, the next most common outcome was death because of pulmonary complication, and this was significantly more likely if the patient needed ventilation support in PICU. Similar findings related to incidence and impact have been reported previously,[2,3,7] describing rates of pulmonary complication and mortality from pulmonary complications between 25–36% and 24–65%, respectively. The detail related to survivors in this study has not been detailed in previous studies. Similar risk of mortality related to the need for PICU admission (because of all causes) in children post-HCT was reported in a recently published large multicentre study by Zinter and colleagues, which showed survival was reduced to 52.5% at 1 year in those who required a PICU admission.[17]

The risk factor analysis in this study highlighted several factors related to the patient pre-transplant, including pre-existing pulmonary disease and the presence of an abnormal chest CT scan associated with a higher risk of developing

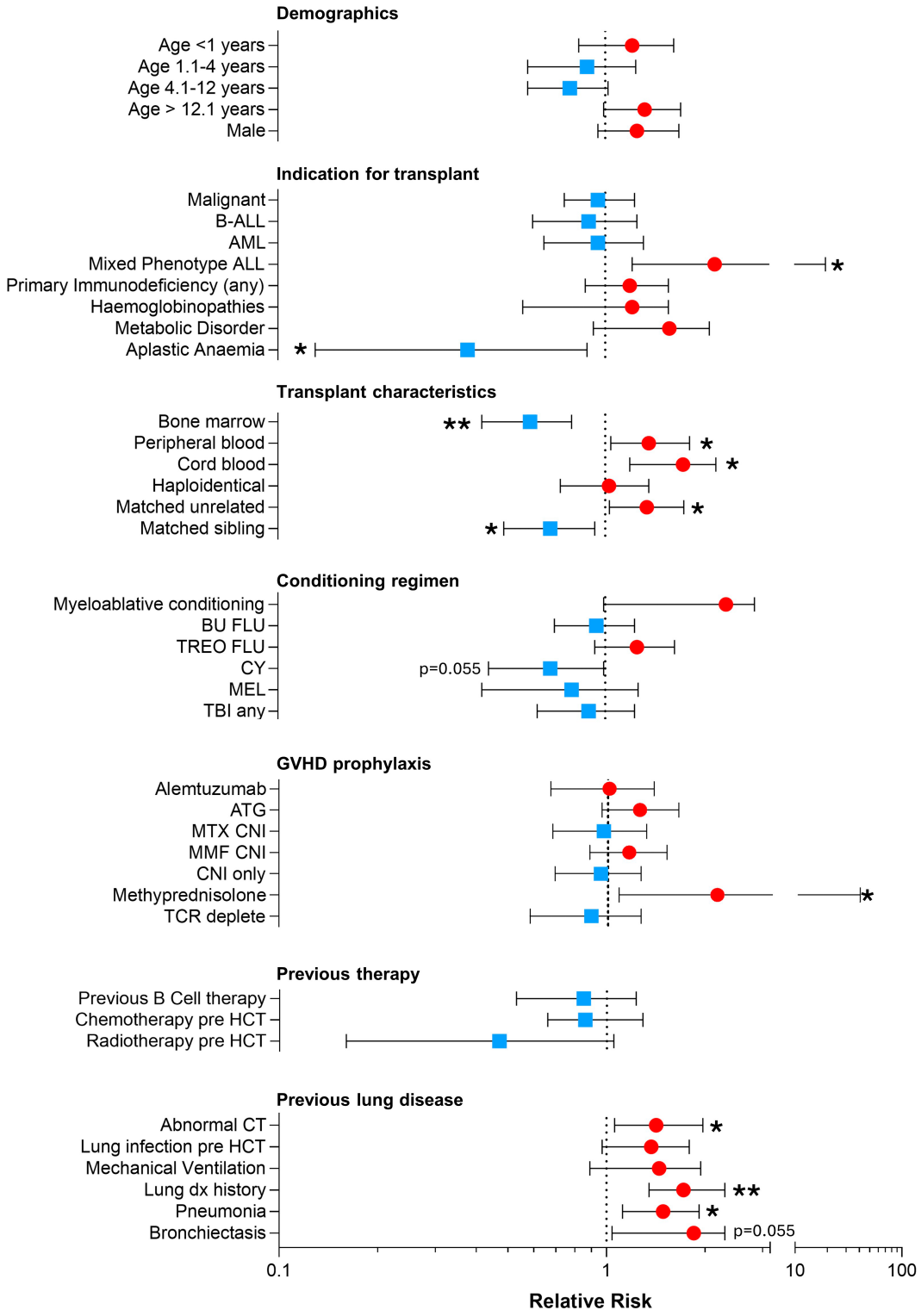

Figure 3. Risk factors for the development of post-HCT pulmonary complications. Forrest plot demonstrating risk factors and protective factors pre transplant and related to indication for transplant, previous lung disease, donor characteristics, conditioning regimen and GVHD prophylaxis. Relative risk with 95% confidence interval shown, *$P < 0.05$ and **$P < 0.01$.

pulmonary disease post-HCT. This demonstrates the importance of understanding a child's exposure to specific pulmonary disease and the importance of a pre-HCT baseline chest CT scan, recently endorsed as a recommendation in an updated American Thoracic Society clinical practice guideline related to paediatric BOS.[18] Both can be performed in most children pre-HCT, compared with lung function pre-HCT, which is limited to children old enough and well enough to perform these tests. Consideration of pre-HCT consultation with a paediatric respiratory physician may also be beneficial in this high-risk group of patients. Patients who received a transplant that was from a matched sibling donor using bone marrow as the source had the lowest risk of developing post-transplant pulmonary disease, and this is reflective of the low NRM reported in this group. Unfortunately, the majority of patients do not have a matched sibling donor available, and further research is required to identify why having a MUD is related to increased risk of pulmonary complications. Another factor associated with a decreased risk of developing post-HCT pulmonary disease was a diagnoses of aplastic anaemia. This is likely related to the reduced intensity conditioning regimen, use of bone marrow as a cell source and matched sibling as a donor preference (compared with a trial of immunotherapy).

Interestingly, in this cohort, there was no difference in rates of acute GVHD between the group who developed post-HCT pulmonary disease compared with those who do not. In contrast, cGVHD rates were higher in the group who developed post-HCT pulmonary disease, which has been shown in an earlier study.[7] It is important to highlight cGVHD often occurred after the onset of pulmonary complications had become clinically apparent and included some patients who received a diagnoses of BO, a type of cGVHD. This finding suggests there may be donor versus host interactions early in transplant whose aetiology overlaps with both the development of cGVHD and the development of pulmonary complications.

Several risk factors previously reported to increase a patient's risk of post-HCT pulmonary disease related to specific conditioning agents in adults[12] including TBI (high or low dose) were not statistically significant in this cohort. This may have been because of relatively small sample size and variety of conditioning regimens used, with multiple combinations of chemotherapy ± radiation. A recent systematic review looked at pulmonary complications post-TBI in children and identified six studies that reported on non-infectious pulmonary complications, particularly IPS in this group.[19] This review[19] also did not identify an association between TBI and IPS as a single factor but highlighted that multiple variables may have contributed to this finding including the following: systemic chemotherapy agents that carry different risk profiles, limitations on reporting of lung point dose, variations in dose rate and contribution from graft- vs host-related factors. Compared with previously published single-centre retrospective studies,[2–4,7] this study was conducted in a comparatively large population size, was performed across more than one centre, included only children who underwent allogeneic transplant (compared with both autologous and allogeneic) and is the first described for the Australian cohort. Overall, the risk factor analysis highlights that no single factor causes pulmonary disease in isolation, but the culmination of factors pre- and post-HCT.

This study's limitations include its retrospective nature and potential underreporting of less severe pulmonary complications managed outside the tertiary centre. Data from patients aged 18 or older who transitioned to adult care or were treated interstate may have also been missed. The classification of pulmonary complications was subject to investigator bias; however, all positive microbiological pulmonary investigations were collected, and diagnoses were classified as infective, non-infective or both using the definitions described in Supplementary table 1. The sample size was insufficient for multivariate analysis of risk factors, an area for future research requiring a substantial increase in patient numbers for meaningful significance.

The risk factor analysis performed in this study identifies potential preventative and therapeutic strategies for managing children at risk of post-HCT pulmonary complications. Prior to HCT, strategies could include early multidisciplinary involvement of at-risk patients, such as involvement by infectious disease, respiratory and transplant teams to establish a pre-emptive plan for therapy should the patient develop a post-HCT pulmonary complication. The role of pre- and post-transplant chest physiotherapy is also an area that requires consideration of implementing in children old enough to participate. A recently published study in adults showed a significant improvement in lung function in those who were randomised to receive chest physiotherapy in the

3 weeks prior to HCT admission.[20] Whether this translates to children and leads to a reduction in post-transplant pulmonary complications requires further research but is an appealing and low-risk strategy that could be incorporated into clinical care.

Education for patients, families and clinical staff who care for these patients on the subtle early signs and symptoms of these pulmonary complications is also an important strategy to improve awareness. Prevention of infectious complications post-HCT involves a combination of pre-emptive screening and pharmacological methods, including antiviral prophylaxis and antifungal prophylaxis. In this study, the most used antifungal agents, fluconazole or micafungin, have inferior mould cover in comparison with posaconazole and voriconazole. In patients with an increased risk of post-HCT pulmonary complications such as an abnormal CT chest or who have had previous lung disease, it is possible they may benefit from antifungal prophylaxis with broader mould coverage. This requires further prospective studies and the interactions with CNI require dose adjustment considerations in the setting of azole antifungal use.

Because of the prevalence of CMV in the patients who died because of pulmonary disease, post-HCT prophylaxis strategies for this cohort to reduce severe CMV disease are required. There is established evidence for the use of letermovir prophylaxis in CMV seropositive patients for the reduction in post-HCT mortality.[21] This is increasing in paediatric populations, and some centres have adopted the use of letermovir in high-risk groups (recipient +/donor −) based on safety and efficacy of its use off label.[22] Letermovir is not currently approved in Australia for children but is available through direct access schemes.

In terms of improved treatment strategies, more research is required into the biological drivers of paediatric non-infectious pulmonary complications, to identify targeted strategies that minimise the need for prolonged high-dose steroids. A current example is the use of etanercept, a TNFα inhibitor, used as a treatment in children with IPS, because of the identification of elevated TNFα levels in BAL and plasma of patients with this complication.[23] Aside from IPS and Ta-TMA (target agent eculizumab), there is limited evidence for survival benefit of targeted therapies for this group of non-infectious pulmonary complications. Certain pulmonary complications post-HCT, such as DAH with dismal survival, are at most urgent need of improved therapeutic strategies.[24]

Pulmonary complications as a group of disorders are heterogenous and encompass a variety of different diagnoses. This study shows that a significant proportion of paediatric patients experienced more than one pulmonary complication and that the aetiology of the pulmonary disease is complex. This highlights the challenge for clinicians caring for these patients and that there are factors downstream that continue to influence patient outcomes. For example, studies have shown the presence of a virus in the respiratory tract pre-HCT (e.g. rhinovirus) may 'prime' the pulmonary system to be more at risk of being a target for post-transplant graft versus host interactions and non-infectious pulmonary diseases such as IPS.[25] This relationship may be bidirectional, for example treatment of many non-infectious pulmonary diseases utilised corticosteroids, which may increase the risk of developing and/or worsening infective complications in these patients. Rather than defining a patient as having infectious or non-infectious pulmonary disease, a more meaningful approach may be to consider the many factors (both microbiological and transplant-related) that lead to pulmonary disease manifestation. This study shows that pulmonary complications remain an important cause of morbidity and mortality in children post-HCT, and clinicians need to have a high index of suspicion for their development in this population.

METHODS

Cohort description and clinical definitions

This was a retrospective study of children (age < 18 years) who underwent allogeneic HCT between 2016 and 2022 at the Royal Children's Hospital, Melbourne or Perth Children's Hospital, Western Australia. Patient episodes of transplant were identified using the Australian bone marrow transplant registry and Australian Bone Marrow Database registry (ABMDR). Relevant patient demographic, transplant and pulmonary complication episode data were collected retrospectively from both the electronic medical record (EMR) and written medical records. Local institutional ethics committee approval was obtained at the Royal Children's Hospital for this study, HREC reference 91777.

Pulmonary complications were defined as signs and symptoms of pulmonary disease (including tachypnoea,

respiratory distress, fever, hypoxia or haemoptysis) and newly developed pulmonary imaging changes [chest x-ray (CXR) or computed topography (CT)] or changes in lung function following allogeneic HCT. Complications were classified as occurring early (first 100 days of post-transplant) or late (after 100 days of post-transplant). Patients were included if they required admission to either the day oncology unit or inpatient ward setting. Pulmonary complications were then further classified as either infectious, non-infectious complications or a combination of both. Infectious complications were classified as either a microbiologically defined infection (MDI) or clinically defined infection (CDI).[26] A MDI was defined as an infection that is clinically detectable and microbiologically proven. Causes of bacterial pneumonia were identified on direct BAL sampling and on peripheral blood cultures. A CDI was defined as a site of infection that is diagnosed but its microbiological pathogenesis cannot be proven or is inaccessible to examination. Non-infectious complications were defined using definitions from the American Thoracic Society, National Institute of Health (NIH) and expert consensus definitions and are detailed in Supplementary table 1.[6,8,27] Pulmonary complications were classified as severe based on the following outcome data: if a patient required oxygen therapy, intensive care admission, developed chronic lung disease or died because of the pulmonary complication. Outcomes of pulmonary complications were also measured longitudinally at 1, 3 and 6 months post onset of symptoms. Children were followed up for a minimum of 8 months or until transitioned to an adult centre or until the end of 2022 whichever occurred latest. General transplant outcomes including rates of acute GVHD (Seattle criteria[28]), chronic GVHD (NIH criteria[29]), veno-occlusive disease (VOD) (EBMT Paediatric Criteria[30]) and transplant-associated thrombotic microangiopathy (TA-TMA) (Modified Jodele criteria[31]) were also collected.

Infection prophylaxis

Patients in this study were admitted in high efficiency particulate absorbing (HEPA) filtered, positive pressure single rooms for the duration of the conditioning regimen up until a minimum of 30 days post Day 0. Data were collected on initial antifungal, antiviral and antibiotic prophylaxis [including for *Pneumocystis jirovecii* pneumonia (PJP)] prescribed at the time of admission for HCT. Investigation for infection included bacterial microscopy and culture, fungal culture and viral respiratory polymerase chain reaction (PCR). Respiratory multiplex PCR panel included the following: rhinovirus, coronavirus, mycoplasma pneumonia, bordetella pertussis, human metapneumovirus, adenovirus, human parainfluenzae 1–4, parechovirus, enterovirus, respiratory syncytial virus and influenza A and B. Fungal infections were classified as proven, probable and possible according to EORTC criteria.[32]

Data analysis

Statistical analyses were performed in GraphPad Prism version 10. Qualitative variables are described as numbers and percentage (%), and continuous variables are reported as medians and interquartile range (IQR). The pre-transplant and transplant characteristics were compared between patients who developed a pulmonary complication or not, via Fisher's exact *t*-test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Univariate analysis to determine relative risk and 95% confidence interval was calculated using Koopman asymptotic score. This was based on characteristics pre and during the first transplant episode only and is visualised using the Forest plots including 95% confidence intervals. Pulmonary complication types and characteristics were collected on patients following the first transplant episode through and inclusive of the second transplant episode (if applicable) up until the end of 2022, or until the patient was transferred to another centre for example in the setting of transition to adult care or death. Survival rates were estimated using the Kaplan–Meyer method, differences were assessed using the log rank test, and hazard ratio was calculated using the Mantel–Haenszel method. For all analyses, a P-value < 0.05 was considered significant.

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AUTHOR CONTRIBUTIONS

Hannah Walker: Conceptualization; data curation; formal analysis; methodology; project administration; resources; visualization; writing – original draft; writing – review and editing. **Joanne Abbotsford:** Data curation; writing – review and editing. **Gabrielle M Haeusler:** Conceptualization; methodology; supervision; writing – review and editing. **Daniel Yeoh:** Conceptualization; methodology; supervision; writing – review and editing. **Shanti Ramachandran:** Methodology; supervision; writing – review and editing. **Michelle Ng:** Writing – review and editing. **Jonathan Holzmann:** Data curation; writing – review and editing. **Shivanthan Shanthikumar:** Methodology; supervision; writing – review and editing. **Heather Weerdenburg:** Data curation; writing – review and editing. **Diane Hanna:** Methodology; supervision; writing – review and editing. **Melanie R Neeland:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; supervision; visualization; writing – original draft; writing – review and editing. **Theresa Cole:** Conceptualization; methodology; supervision; writing – review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author.

These data are not publicly available because of privacy or ethical restrictions.

REFERENCES

1. Elbahlawan L, McArthur J, Morin CE *et al*. Pulmonary complications in children following hematopoietic cell transplantation: A case report and review of the diagnostic approach. *Front Oncol* 2021; **11**: 772411.
2. Çıkı K, Doğru D, Kuşkonmaz B *et al*. Pulmonary complications following hematopoietic stem cell transplantation in children. *Turk J Pediatr* 2019; **61**: 59–60.
3. 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 Transplant* 2009; **15**: 817–826.
4. Choi YH, Jeong HJ, An HY *et al*. Early predictors of mortality in children with pulmonary complications after haematopoietic stem cell transplantation. *Pediatr Transplant* 2017; **21**: 13062.
5. Fitch T, Myers KC, Dewan M, Towe C, Dandoy C. Pulmonary complications after pediatric stem cell transplant. *Front Oncol* 2021; **11**: 755878.
6. Williams KM. Noninfectious complications of hematopoietic cell transplantation. *Hematology Am Soc Hematol Educ Program* 2021; **2021**: 578–586.
7. Eikenberry M, Bartakova H, Defor T *et al*. Natural history of pulmonary complications in children after bone marrow transplantation. *Biol Blood Marrow Transplant* 2005; **11**: 56–64.
8. Tamburro RF, Cooke KR, Davies SM *et al*. Pulmonary complications of pediatric hematopoietic cell transplantation a National Institutes of Health workshop summary. *Ann Am Thorac Soc* 2021; **18**: 381–394.
9. Ueda K, Watadani T, Maeda E *et al*. Outcome and treatment of late-onset noninfectious pulmonary complications after allogeneic haematopoietic SCT. *Bone Marrow Transplant* 2010; **45**: 1719–1727.
10. Whittle AT, Davis M, Shovlin CL, Ganly PS, Haslett C, Greening AP. Alveolar macrophage activity and the pulmonary complications of haematopoietic stem cell transplantation. *Thorax* 2001; **56**: 941–946.
11. Schindera C, Usemann J, Zuercher SJ *et al*. Pulmonary dysfunction after treatment for childhood cancer comparing multiple-breath washout with spirometry. *Ann Am Thorac Soc* 2021; **18**: 281–289.
12. Vogel J, Hui S, Hua CH *et al*. Pulmonary toxicity after total body irradiation – critical review of the literature and recommendations for toxicity reporting. *Front Oncol* 2021; **11**: 708906.
13. Lucena CM, Torres A, Rovira M *et al*. Pulmonary complications in hematopoietic SCT: A prospective study. *Bone Marrow Transplant* 2014; **49**: 1293–1299.
14. Fraebel J, Engelhardt BG, Kim TK. Noninfectious pulmonary complications after hematopoietic stem cell transplantation. *Transplant Cell Ther* 2023; **29**: 82–93.
15. Peters C, Dalle JH, Locatelli F *et al*. Total body irradiation or chemotherapy conditioning in childhood ALL: A multinational, randomized, noninferiority phase III study. *J Clin Oncol* 2021; **39**: 295–307.
16. Passweg JR, Baldomero H, Bader P *et al*. Use of haploidentical stem cell transplantation continues to increase: The 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant* 2017; **52**: 811–817.
17. Zinter MS, Brazauskas R, Strom J *et al*. Intensive care risk and long-term outcomes in pediatric allogeneic hematopoietic cell transplant recipients. *Blood Adv* 2024; **8**: 1002–1017.
18. Shanthikumar S, Document S, Gower WA *et al*. Detection of bronchiolitis obliterans syndrome following pediatric hematopoietic stem cell transplantation. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2024; **210**: 262–280.
19. Ehler ED, Turcotte LM, Skamene S *et al*. Idiopathic pneumonitis syndrome after total body irradiation in pediatric patients undergoing myeloablative hematopoietic stem cell transplantation: A PENTEC comprehensive review. *Int J Radiat Oncol Biol Phys* 2024; **119**: 625–639.
20. Waked IS, Ibrahim ZM, Alkhamees N, Rashad AH. Effects of pre-transplant chest physical therapy on spirometric values and respiratory muscle strength in patients waiting for allogeneic hematopoietic stem cell transplantation: A randomized controlled trial. *Arch Med Sci* 2024; **20**: 104–112.
21. Ljungman P, Schmitt M, Marty FM *et al*. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Clin Infect Dis* 2020; **70**: 1525–1533.
22. Galaverna F, Baccelli F, Zama D *et al*. Letermovir for cytomegalovirus infection in pediatric patients undergoing allogenic hematopoietic stem cell transplantation: A real-life study by the infectious diseases working group of Italian Association of Pediatric Hematology-Oncology (AIEOP). *Bone Marrow Transplant* 2024; **59**: 505–512.
23. Yanik GA, Grupp SA, Pulsipher MA *et al*. TNF-receptor inhibitor therapy for the treatment of children with idiopathic pneumonia syndrome. A joint pediatric blood and marrow transplant consortium and children's oncology group study (ASCT0521). *Biol Blood Marrow Transplant* 2015; **21**: 67–73.
24. Wu J, Fu HX, He Y *et al*. Risk factors and outcomes of diffuse alveolar haemorrhage after allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2021; **56**: 2097–2107.
25. Versluys B, Bierings M, Murk JL *et al*. Infection with a respiratory virus before hematopoietic cell transplantation is associated with alloimmune-mediated lung syndromes. *J Allergy Clin Immunol* 2018; **141**: 697–703.e698.
26. Haeusler GM, Phillips RS, Lehrnbecher T, Thursky KA, Sung L, Ammann RA. Core outcomes and definitions for pediatric fever and neutropenia research: A consensus statement from an international panel. *Pediatr Blood Cancer* 2015; **62**: 483–489.
27. Jodele S, Davies SM, Lane A *et al*. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: A study in children and young adults. *Blood* 2014; **124**: 645–653.

28. Harris AC, Young R, Devine S *et al*. International, multicenter standardization of acute graft-versus-host disease clinical data collection: A report from the Mount Sinai acute GVHD international consortium. *Biol Blood Marrow Transplant* 2016; **22**: 4–10.
29. Jagasia MH, Greinix HT, Arora M *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 Transplant* 2015; **21**: 389–401.e381.
30. Fussiova M, Svec P, Horakova J *et al*. The importance of new EBMT criteria on the diagnosis of veno-occlusive liver disease in children. *J Clin Med* 2023; **12**: 826.
31. Schoettler ML, Carreras E, Cho B *et al*. Harmonizing definitions for diagnostic criteria and prognostic assessment of transplantation-associated thrombotic microangiopathy: A report on behalf of the European Society for Blood and Marrow Transplantation, American Society for Transplantation and Cellular Therapy, Asia-Pacific Blood and Marrow Transplantation Group, and Center for International Blood and Marrow Transplant Research. *Transplant Cell Ther* 2023; **29**: 151–163.
32. Donnelly JP, Chen SC, Kauffman CA *et al*. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of cancer and the mycoses study group education and research consortium. *Clin Infect Dis* 2020; **71**: 1367–1376.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.