

Early predictors of mortality in children with pulmonary complications after haematopoietic stem cell transplantation

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Abstract

PC are a main cause of death following HSCT in children. We aimed to evaluate early predictors of mortality in paediatric recipients with PCs. A retrospective observational study of 35 patients with 49 episodes of PI on chest radiography (of 124 patients) who had undergone HSCT at a tertiary university hospital between January 2011 and December 2012 was performed. During follow-up (median 26.1 months), 15 episodes led to death (30.6%). An aetiologic diagnosis was made by non-invasive tests in 24 episodes (49.0%) and by adding bronchoalveolar lavage and/or lung biopsy in 7 episodes with diagnostic yield (77.8%, $P = .001$). Thus, a specific diagnosis was obtained in 63.3% of the episodes. Aetiology identification and treatment modification after diagnosis did not decrease mortality ($P = .057$, $P = .481$). However, the number of organ dysfunctions at the beginning of PI was higher in the mortality group, compared to the survivor group (1.7 ± 1.2 vs 0.32 ± 0.59 ; $P = .001$). Hepatic dysfunction (OR, 11.145; 95% CI, 1.23 to 101.29; $P = .032$) and neutropaenia (OR, 10.558; 95% CI, 1.07 to 104.65; $P = .044$) were independently associated with risk of mortality. Therefore, hepatic dysfunction and neutropaenia are independent early predictors of mortality in HSCT recipients with PCs.

KEYWORDS

children, hematopoietic stem cell transplantation, lung diseases, mortality

1 | INTRODUCTION

With the increasing indication of HSCT over the past decade and improvements in short-term survival, concerns have grown about the adverse effects of HSCT. PCs with infectious or non-infectious causes have been recently reported to occur in 20%–30% of adult and paediatric HSCT recipients and are usually related with poor outcomes.^{1–4} Various diagnostic tests can be utilized to identify the aetiologies of

PIs for targeted therapy, depending on the condition of recipients with PCs.⁵ However, controversy exists regarding whether a clear diagnosis leads to better outcomes.^{1,2,4,6–10} PCs can eventually cause respiratory failure with mechanical ventilation, and single or multiple organ dysfunctions have been identified as predisposing factors relating to prognosis.^{11–15}

Given that the need for mechanical ventilation and critical care after transplantation is associated with poor outcomes,^{11–19} the conditions

Abbreviations: ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CPR, cardiopulmonary resuscitation; CRP, C-reactive protein; CT, computed tomography; GCV, ganciclovir; GVHD, graft-vs-host disease; HLA, human leucocyte antigen; HSCT, hematopoietic stem cell transplantation; ILD, interstitial lung disease; IPS, idiopathic pneumonia syndrome; IQR, interquartile range; IV, intravenous; LB, lung biopsy; MODS, multiple organ dysfunction syndrome; PC, pulmonary complications; PCR, polymerase chain reaction; PERDS, peri-engraftment respiratory distress syndrome; PICU, paediatric intensive care unit; PI, pulmonary infiltrates; TA-TMA, transplantation-associated thrombotic microangiopathy; VATS, video-assisted thoracoscopy; VOD, veno-occlusive disease.

that contribute to the deterioration of patients with PCs should be investigated. However, most previous studies have reported on factors related to PC development, focusing on preventive strategies. Thus, few studies currently exist regarding the early predictors of respiratory failure and death associated with PCs after HSCT.⁴ Therefore, the aim of this study was to evaluate the ability of diagnostic work-ups, final diagnoses, treatment modification, and medical conditions at the time of PC initiation to predict mortality in HSCT recipient children.

2 | PATIENTS AND METHODS

2.1 | Patients

Between January 2011 and December 2012, 128 paediatric patients underwent 144 HSCTs at our hospital. We initially excluded 3 recipients with a loss of graft and 1 recipient who was transferred to another hospital due to the progression of an underlying disease immediately following stem cell infusion. Sixteen patients underwent a second HSCT as a planned transplantation during the study period. In such cases, we considered only the second HSCT. Among the 124 evaluated paediatric patients, PCs were investigated until relapse, death, or December 31, 2015, whichever came first. A total of 49 PI episodes in 35 patients were retrospectively identified during the median follow-up period of 26.1 months (IQR, 2.9-38.4) and were finally included in the present study. This study is in accordance with the Helsinki Declaration of 1975. Institutional review board approval was obtained for this study (2016/08/16).

2.2 | Data collection

Data were collected regarding general characteristics, including transplant-related factors, clinical findings, and outcomes for each PC episode. The general characteristics assessed included age, sex, underlying disease, previous lung problems, the number and type of HSCTs, stem cell source, engraftment day, and human leucocyte antigen compatibility of the allograft. The underlying diseases were categorized as leukaemia/lymphoma, solid tumour, and non-malignant disease, including primary immunodeficiency, aplastic anaemia, and osteopetrosis. Previous lung problems were identified when the patients had an active lung disease at the time of the HSCT infusion. Neutrophil engraftment day was defined as 3 consecutive days with an absolute neutrophil count greater than or equal to 1.0×10^9 cells/L.

A PC was defined as the new development of PIs on chest radiography simultaneously with respiratory symptoms requiring admission for evaluation or treatment. Respiratory symptoms included cough, sputum, dyspnoea, chest pain, blood tinged sputum, and cyanosis. For each PC episode, the time to diagnosis from transplantation, diagnostic procedures applied, time to BAL or LB since PI appearance, and relevant medical conditions were investigated. In addition, changes in the empirical treatment attributable to the results from diagnostic tests were recorded. The evaluation of medical conditions at the time of PI initiation considered the following: the presence of engraftment syndrome, acute GVHD, chronic GVHD, VOD, or CMV infection;

medication being administered; and organ dysfunction, identified using the specific Pediatric Critical Care Medicine criteria published in 2003.²⁰ Criteria for organ dysfunction of the cardiovascular, neurological, haematological, renal, gastrointestinal, and hepatic systems were evaluated, and the data indicating the most severe condition within 48 hours of PI appearance were used. Respiratory dysfunction was excluded from the criteria as arterial blood gas was not frequently measured in children with mild respiratory distress. Acute and chronic GVHDs were assessed as described elsewhere.^{21,22} CMV infection was defined as the need for pre-emptive or curative induction therapy with ganciclovir. Pre-emptive treatment was started with a half-dose therapy of ganciclovir when the CMV antigenemia assay results showed 1 to 10 antigen-expressing cells/200 000 polymorphonuclear leucocytes, and induction therapy was started when the results showed more than 10 antigens expressing cells/200 000 polymorphonuclear leucocytes. For drugs already being administered, we noted the following: antibiotics or antifungal agents intravenously injected; inotropic or vasopressors; and immunosuppressants including tacrolimus, cyclosporine, mycophenolate mofetil, and steroids as prophylaxis or treatment of transplantation-related complications. According to the analysis of accompanying medical conditions, an early predictor of mortality was defined as a statistically significant comorbidity occurring with PCs within 48 hours of PI initiation.

The outcome of each episode was considered in terms of the number of admissions to the PICU, unexpected events such as CPR or unplanned transfer to the PICU, and survival to hospital discharge. Cause of death was clarified as related to the PI or not, and non-survivors included only those patients who died as a result of PCs. For that reason, two patients who died were classified into the survivor group, because they died due to the recurrence of underlying disease.

2.3 | Diagnostic evaluations

PIs were evaluated using non-invasive and/or invasive work-ups. The non-invasive tests included blood cultures, sputum examination, serology tests, chest CT scans, echocardiography, and pulmonary function tests. Sputum was collected by expectoration, using nasopharyngeal aspiration, a swab, or transtracheal aspiration if the patient was already intubated. Sputum was Gram stained; cultured for bacteria, virus, and fungi; and subjected to a PCR for viruses and *Mycoplasma pneumoniae*. Additionally, an acid-fast bacillus stain and sputum culture were performed when a high suspicion of *Mycobacterium tuberculosis* infection existed. For serology tests, the CMV antigen test or viral load, aspergillus antigen test, and mycoplasma antibody were assessed.

As invasive tests, BAL and LB were arranged based on a joint discussion between an oncologist, pulmonologist, intensivist, and radiologist. BAL was performed by a paediatric pulmonologist using an age-adjusted flexible bronchoscope. Sterile normal saline was instilled in 2 aliquots of 10 to 20 mL, which was suctioned and sent for pathology and microbiology evaluation. VATS LBs were performed by paediatric thoracic surgeons and ultrasound-guided LBs were performed by a paediatric radiologist. All biopsy and BAL samples were screened for infectious pathogens with Gram, acid-fast, Gomori methenamine

silver stains, and viral immunostains. Samples were also processed for bacteria, viruses, and fungi cultures. The PCR for *Mycobacterium*, CMV, and respiratory virus including respiratory syncytial virus, metapneumovirus, parainfluenza, influenza, rhinovirus, and adenovirus was additionally performed using BAL fluid. An immunofluorescence assay and PCR for the detection of *Pneumocystis jiroveci* were also utilized.

2.4 | Diagnostic definitions

Diagnoses were based on clinical, radiologic, microbiologic, and pathologic findings and were thoroughly reviewed by two of the authors (YHC and JDP).²³ All diagnoses were classified as definite, probable, or non-diagnostic as follows. Definite bacterial pneumonia was defined as BAL fluid containing the identified pathogen in an amount $>10^4$ CFU/mL. Definite viral pneumonia was defined as detection of the virus in histopathology. Probable viral pneumonia was defined as the discovery of a virus in PCR or culture of BAL fluid or sputum collected from patients with clinical features consistent with viral pneumonia. A positive test for CMV by antigenemia in plasma or PCR in a respiratory specimen alone was not regarded as CMV pneumonia.²⁴ Fungal pneumonia was established based on definitions from the consensus of the European Organization for Research and Treatment of Cancer/Invasive Fungal infections Cooperative Group.²⁵ A definite diagnosis of *P. jiroveci* pneumonia was made by the identification of *P. jiroveci* from BAL or lung tissue, while a probable diagnosis was made from expectorated or aspirated sputum.²⁶ *M. tuberculosis* was diagnosed as a positive result on the acid-fast bacillus stain and culture in a respiratory specimen.²⁶

For non-infectious PCs, the following diagnoses were confirmed: IPS, non-cardiogenic pulmonary oedema and/or pleural effusion, PERDS, lung GVHD, transfusion-related acute lung injury, and ILD. IPS was defined as diffuse alveolar damage in the absence of identifiable infectious aetiologies on histologic examination.²⁷ ILD was defined in a similar manner to IPS, but was characterized by a different injury site and clinical features as according to recent study.²⁸ PERDS was considered in the presence of fever and evidence of pulmonary injury in the form of hypoxia ($SpO_2 < 90\%$) and/or infiltrates on chest radiographs in the absence of clinical cardiac dysfunction.²⁹ To be diagnosed with PERDS, the symptoms and/or the radiographic findings had to have occurred within 5 days of neutrophil engraftment.²⁹ Lung GVHD was diagnosed primarily by the presence of obstructive pulmonary dysfunction based on pulmonary function tests, and accompanied by chest CT findings of areas showing patchy infiltration, bronchial dilatation, and hypo-attenuation or increased density.³⁰ Transfusion-related acute lung injury was identified whenever a patient developed a hypoxemic respiratory insufficiency during, or shortly after, transfusion of any blood product, according to outlined diagnostic criteria.³¹ Pulmonary oedema and/or pleural effusion was defined as the presence of characteristic infiltrates or fluid within pleural spaces, negative cultures, and beneficial response to diuresis without cardiac dysfunction and excluding the above-mentioned lung problems.³²

2.5 | Statistical analysis

Statistical analyses were performed using SPSS software (version 22; SPSS Inc., IBM, Armonk, NY, USA). Qualitative variables are described as numbers (%). Continuous variables are reported as means (\pm SD) or medians (IQR). The general characteristics were compared between survivors and non-survivors via a chi-square test or Fisher's exact test for categorical data, and via a t-test for continuous data. Logistic regression was performed to identify variables that were significantly associated with poor outcomes for each PI episode as assessed by an estimated odds ratio (OR) and 95% confidence interval (CI). Variables that showed a significant univariate result ($P < .05$) were included in a multivariate logistic regression. A multivariate model was constructed with forward stepwise methods using threshold P -values of .10 for removal or .05 for addition to the model. Survival was estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test.

3 | RESULTS

3.1 | Patients' characteristics

The general characteristics of the 35 recipients (25 males and 10 females) with one or more PI episode following HSCT are summarized in Table 1. The median age was 10.5 years (IQR, 4.8 to 14.0). Over half of the patients had leukaemia and lymphoma (60.0%), and 16 recipients (45.7%) had a lung problem prior to HSCT including infectious disease ($n = 6$), non-infectious disease ($n = 7$), and cancer ($n = 2$). Most of the patients had undergone only one HSCT, while 7 had received two or more HSCT. The majority of the HSCT procedures were allogeneic (60.0%), and the most common stem cell source for allogeneic transplantation originated from peripheral blood (60.9%). The median number of days to neutrophil engraftment was 10 days (IQR, 10 to 12) after transplantation. In addition, 10 recipients had more than two PI episodes during the median 26.1 months of follow-up (IQR, 2.9 to 38.4). There were no statistically significant differences in general or transplantation-related characteristics between survivors and non-survivors, except for the length of the follow-up period.

3.2 | Diagnoses

A total of 49 episodes of lung infiltrates were investigated in the 35 recipients during the follow-up period. Among the diagnostic PI evaluations, PCR for virus detection in collected sputum was the most commonly conducted test (45 episodes; 91.8%). Blood culture and the serum *Aspergillus* antigen test were the next most commonly used tests (44 episodes; 89.8%, 41 episodes; 83.7%). Chest CT was performed when PI was first suspected in 40 episodes (81.6%; IQR, 0-2). As the non-invasive tests, CMV antigenemia or viral load and mycoplasma antibody were commonly checked in 34 episodes (69.4%) and 36 episodes (73.5%). However, sputum examination for bacteria and *Pneumocystis jiroveci* were

TABLE 1 Clinical characteristics

	Total (n = 35) n (%)	Survivor (n = 20) n (%)	Non-survivor (n = 15) n (%)	P-value
Age (y)	10.5 (4.8-14.0)	9.0 (2.3-15.0)	7.2 (1.3-12.8)	.541
Male	25 (71.4)	16 (80.0)	9 (60.0)	.202
Diagnosis				.134
Solid tumour	8 (22.9)	6 (30.0)	2 (13.3)	
Hemato-oncologic disease	21 (60.0)	12 (60.0)	9 (60.0)	
Non-malignancy ^a	6 (17.1)	2 (10.0)	4 (26.7)	
Previous lung disease ^b	16 (45.7)	8 (40.0)	8 (53.3)	.435
Pre-HSCT radiotherapy including lung	6 (17.1)	2 (10.0)	4 (26.7)	.377
Number of HSCT (≥2)	7 (20.0)	4 (26.7)	3 (15.0)	.398
HSCT type				.076
Autologous	12 (34.3)	10 (50.0)	2 (13.3)	
Haploidentical	2 (5.7)	1 (5.0)	1 (6.7)	
Allogenic	21 (60.0)	9 (45.0)	12 (80.0)	
Related	6 (28.5)	3 (30.0)	3 (23.1)	.899
Unrelated	15 (71.4)	6 (60.0)	9 (69.2)	
Stem cell source of allogenic HSCT				.144
Peripheral	14 (60.9)	7 (70.0)	7 (53.8)	
Bone marrow	5 (21.7)	3 (30.0)	2 (15.4)	
Cord	4 (17.4)	0	4 (30.8)	
HLA match 10/10	10 (28.5)	5 (62.5)	5 (41.7)	.330
Engraftment days	10.0 (10.0-12.0)	10.0 (10.0-13.5)	11.0 (10.0-12.0)	.300
PI episodes (≥2)	10 (28.6)	7 (35.0)	3 (20.0)	.458
Follow-up period (mo)	26.1 (2.9-38.4)	36.4 (27.7-43.9)	2.9 (1.5-5.1)	<.001

^aAplastic anaemia (n = 1), osteopetrosis (n = 1), chronic granulomatous disease (n = 1), congenital neutropaenia (n = 2), severe combined immunodeficiency (n = 1).

^bInfectious pneumonia (n = 7), non-infectious disease including bronchiolitis obliterans, lung fibrosis, restrictive lung disorder confirmed by pulmonary function test (n = 7), cancer (n = 2).

only conducted in 20 episodes (40.8%), and 16 episodes (32.7%). BAL was performed in 9 episodes at a median time of 2.0 days (IQR, 1.0-8.0) after a PI was visible. LB was conducted in 5 episodes at a median time of 7.0 days (IQR, 3.5-8.5). Additionally, 3 episodes were evaluated by both BAL and LB. After invasive tests, prolonged air leakage developed in one patient who had undergone VATS biopsy. However, there were no cases with procedure-related death.

Using non-invasive tests, specific aetiologies were discovered in almost half of the PI episodes (24 episodes, 49%; Figure 1). Among these, two episodes included additional invasive tests, which did not show further useful information. However, 7 of the 25 episodes without pathogen discovered through non-invasive tests were given an aetiological diagnosis by adding BAL and/or LB, resulting in a diagnostic yield (77.8%, $P = .001$).

Finally, after vigorous diagnostic investigations, infectious causes were diagnosed in 17 episodes (34.7%), and non-infectious causes were diagnosed in 14 episodes (28.6%). However, about one-third of PCs were not identified (18 episodes, 36.7%; Table 2). In infectious PCs, viral pneumonia was the most commonly identified aetiology (13

episodes), and one of three patients with parainfluenza viral infection experienced TA-TMA at the same time. Among the non-infectious PCs, pulmonary oedema and/or pleural effusion without heart dysfunction, and lung GVHD were found in 4 episodes each. In this study, no patients were diagnosed with cryptogenic organizing pneumonia, bronchiolitis obliterans syndrome, or diffuse alveolar haemorrhage after diagnostic work-ups.

3.3 | Early predictors of mortality in children with PIs after HSCT

Among transplantation-related complications present at the beginning of the PI, VOD had a higher incidence in the non-survivor group compared to that in the survivor group (2.9% vs 33.3%; $P = .015$; Table 3). In addition, among the medications being administered, intravenous antibiotics, CMV treatment, and intravenous antifungal agent usages were higher in non-survivor mortality group compared to that in the survivor group (P 's < .05). The number of multi-organ dysfunctions at the initiation of PI was higher in the non-survivor group compared to that in the survivor group (0.3 ± 0.6

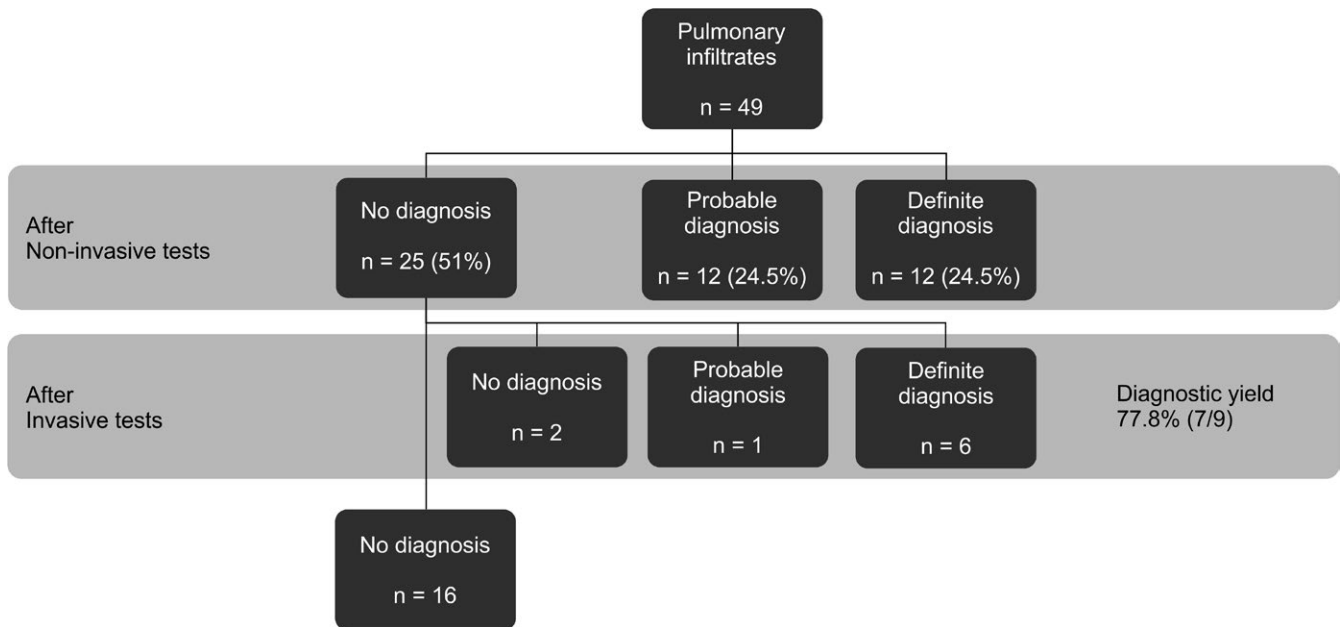


FIGURE 1 Aetiology identification and the diagnostic yield of non-invasive and invasive tests performed in children with PI after hematopoietic stem cell transplantation are depicted. After non-invasive tests, aetiological diagnosis was confirmed in almost half of the episodes (49%). Among episodes with negative results on non-invasive tests, invasive tests were additionally performed in 9 episodes, which showed a higher diagnostic yield (77.8%) compared to that for the non-invasive tests ($P = .001$). Finally, 63% of PI were aetiologically identified

vs 1.7 ± 1.2 ; $P = .001$). In terms of organ dysfunction at the time of PI, haematologic and hepatic dysfunctions were specifically related to mortality. As representatives of haematologic dysfunction, the absolute neutrophil count level and platelet count were lower in the non-survivor group compared to those in the survivor group (5282 vs 2168 , $P = .004$; 138 vs 62 , $P = .020$, respectively). In addition, the platelet level was lower in episodes with MODS compared to that in episodes without MODS (median $27 \times 10^3/\mu\text{L}$ vs $134 \times 10^3/\mu\text{L}$, $P = .003$). When controlling other factors in the multivariate analysis, hepatic dysfunction (OR, 11.145; 95% CI, 1.23 to 101.29; $P = .032$) and neutropaenia (OR, 10.558; 95% CI, 1.07 to 104.65; $P = .044$) were significant independent risk factors of mortality (Table 4). Neutropaenia was significantly associated with poor outcome among infectious causes, but not among non-infectious causes ($P = .005$ vs $P = .207$). Figure 2 shows the overall survival rates of patients without either haematological and hepatic dysfunction, patients with one dysfunction, and patients with both of them (92.9% vs 41.7% vs 0%, $P < .001$). In contrast, aetiology, confirmed diagnosis with invasive work-up, and treatment modification based on the evaluations did not show a significant effect on the prognosis. The model to predict mortality was well calibrated with a Hosmer-Lemeshow test P -value of .969.

All the patients in the non-survivor group required admission to the PICU compared to only 17.6% of the patients in the survivor group. PICU readmission within 7 days after discharge was also more frequently observed in the non-survivor group (2.9% vs 40%, $P < .001$); however, the length of the period from PI identification to PICU admission was not significantly different between groups.

4 | DISCUSSION

In this retrospective study of PI causing respiratory symptoms and requiring admission in paediatric HSCT recipients, PCs were common (occurring in 28% of recipients), and patients with PCs had a high mortality rate (about 43%). After diagnostic work-ups, aetiologies could be identified in 63.3% of episodes, and invasive testing significantly improved diagnostic yields. In an extensive investigation of comorbidities, hepatic dysfunction and neutropaenia within 48 hours of PC detection was associated with mortality, regardless of aetiology. In contrast, the final definite or probable diagnosis and associated treatment modification were not associated with the outcome.

To identify infectious PCs, respiratory specimens are typically inspected first. Expecterated sputum from older children and adolescents may be useful; however, samples from the nasopharynx and throat have no predictive value for bacterial cultures.³³ Because of this, in our study, Gram stain and culture of sputum was conducted in only 45% of episodes while a viral study was conducted in 90% of episodes. To differentiate infectious aetiologies, indirect tests were additionally performed (such as serology and radiologic evaluations) in over 80% of episodes. Recently, several authors have emphasized the importance of high-resolution CT in the diagnosis of PCs after HSCT. However, specifying PC types on the basis of a CT scan alone is difficult, and no specific CT findings exist to indicate treatment modification.^{34,35} Therefore, to precisely distinguish the aetiology of PCs, invasive work-ups with BAL or LB are inevitable. In previous studies, BAL was performed in up to 88% of adult recipients and 43% of paediatric HSCT recipients with 30%-73% diagnostic yields.^{1,2,5,10,36,37} LB also yielded a specific diagnosis in 41%-94% of lung infiltrates,^{5,6,9,37}

TABLE 2 Aetiologic classification

Aetiologies	n
Infectious complication	17 (34.7)
Viral	12
Respiratory syncytial virus	3
Rhinovirus	2
Parainfluenza virus ^a	3
Parainfluenza plus respiratory syncytial virus	1
Parainfluenza plus metapneumovirus	1
Metapneumovirus	1
Coronavirus	1
Bacterial	
<i>Enterococcus faecium</i>	1
<i>Mycobacterium tuberculosis</i> plus <i>Pseudomonas aeruginosa</i>	1
Bacterial plus viral	1
Parainfluenza virus plus <i>Mycoplasma pneumoniae</i>	
Fungal (<i>Mucormycosis</i>)	1
<i>Pneumocystis jirovecii</i>	1
Non-infectious complications	14 (28.6)
IPS	2
Pulmonary oedema and/or pleural effusion	4
PERDS	2
Lung GVHD	4
Transfusion-related acute lung injury	1
ILD	1
Unknown pulmonary complications	18 (36.7)

^aOne of three patients had TA-TMA with viral infection.

especially for non-infectious PCs. The overall diagnostic yield of invasive tests in our study was similar (63.6%) and increased up to 77.8% in the group with negative results on the non-invasive tests. However, the majority of episodes (49%) were diagnosed using the non-invasive tests, and BAL and LB were performed in only 18% and 10% of the total episodes, respectively. Nevertheless, the mortality rate was lower (30.6%) in the present study compared to previous reports of paediatric recipients.^{1,38}

As management of PCs is critically dependent on the possible or presumptive diagnosis, clinicians expect that the identification of specific aetiologies would allow for therapy to be removed, changed, or added, which would lead to survival. Consistent with previous studies,^{2,4,10} we found that the modification of treatment based on examination results (performed in 29 episodes; 60.0%) did not influence the outcome. In contrast, Yoo et al⁸ reported an affirmative effect of therapeutic modification following procedures for diffuse PI causing respiratory failure in cancer patients. However, their study may not generalize to HSCT patients as it was limited to a specialized ICU for critically ill cancer patients. Furthermore, most physicians decide treatment based on not only aetiologic diagnoses, but also responsiveness to empirical treatment and clinical experiences.

Thus, it is difficult to find a direct effect of aetiologic diagnosis and treatment modification on outcomes without consideration of the medical condition. However, the previously mentioned studies on PCs did not analyse comorbidities, which occur in the majority of recipients following transplantation, and may affect treatment choice and outcome. Our study extensively investigated the predictors of outcome through the inclusion of comorbidities, as well as aetiologic diagnosis and treatment modifications. Although our study did not find a relationship between treatment modification and outcome, targeted therapy according to the evaluation result is still recommended (such as early de-escalation antibiotics) and may lead to other positive effects including lower levels of multidrug resistant bacteria and medication toxicity.

Organ dysfunction is a frequent complication in HSCT recipients.³⁹⁻⁴¹ Whether organ dysfunction is a result of high-dose conditioning chemotherapy or transplant-related insult, inflammatory cytokines, such as interleukin-6 and tumour necrosis factor- α , have been suggested as important mediators.^{39,40,42,43} The common pathway leading to organ damage may be a toxic effect of inflammatory cytokines on the vascular endothelium, which leads to a pro-inflammatory and pro-coagulant state. TA-TMA, which has a high mortality rate, is also known to occur as a result of vascular endothelial damage.⁴⁴ In our study, one case with viral pneumonia, coexisting with TA-TMA, died because of MODS. Among several organs, pulmonary, hepatic, and central nervous system dysfunction have shown similar findings in laboratory tests such as low anticoagulant protein C and antithrombin III, and clinical outcomes such as subsequent other organ dysfunction and death.³⁹⁻⁴¹ In the multivariate analysis, organ dysfunction at the beginning of the PI was found to be the most significant prognostic factor in patients with PCs following HSCT. Recipients with PI who also suffered from hepatic dysfunction more frequently had a poor outcome. Half of patients with hepatic dysfunction had co-occurring VOD. Although the number of patients was too small to evaluate outcomes according to the cause of hepatic dysfunction, it could be presumed that VOD, as the common cause of liver dysfunction, might be related to mortality in patients with PCs. In addition, whatever the cause, hepatic dysfunction in an early stage of respiratory distress, rather than in an advanced stage, may aggravate respiratory failure and other organ dysfunction, leading to a poor outcome.

Gordon et al⁴⁵ reported that frequent platelet transfusion, owing to consumptive thrombocytopenia, could be an early marker for subsequent organ dysfunction. In the present study, the platelet level was lower in episodes with MODS compared to that in episodes without MODS; however, thrombocytopenia was not related to final mortality. Instead, neutropaenia was an early prognostic factor of mortality. Unexpected neutropaenia after HSCT results from several causes including infection, GVHD, drug-induced myelosuppression, antibody-mediated neutropaenia, and graft failure.^{46,47} Neutropenic recipients are exposed to the risk of opportunistic infection, which is difficult to overcome and increases mortality. After dividing the patients into two groups by aetiology, neutropaenia was significantly associated with poor

TABLE 3 Univariate analysis of mortality factors

	Survivor (n = 34) n (%)	Non-survivor (n = 15) n (%)	P-value
Days from transplantation to diagnosis of PI	61.5 (25.0-420.0)	41.0 (9.0-82.0)	.073
Transplantation-related complications			
Engraftment syndrome	1 (2.9)	2 (13.3)	.200
Acute GVHD or chronic GVHD ^a	14 (41.2)	7 (46.7)	.721
VOD	1 (2.9)	5 (33.3)	.015
Medication administered			
IV antibiotics	12 (35.3)	12 (80.0)	.007
GCV treatment	4 (11.8)	6 (40.0)	.032
IV antifungal	5 (14.7)	11 (73.3)	<.001
Immunosuppressant (≥3)	10 (45.4)	3 (25.0)	.583
Organ dysfunctions			
Number of organs (mean ± SD)	0.3 ± 0.6	1.7 ± 1.2	.001
Cardiovascular	2 (5.9)	4 (26.7)	.059
Hepatic ^b	3 (8.8)	7 (46.7)	.006
Haematology	4 (11.8)	10 (66.7)	<.001
Kidney	2 (5.9)	2 (13.3)	.392
Brain	0	1 (6.7)	.306
Gastrointestinal	0	1 (6.7)	.306
Laboratory test			
WBC (×10 ³ /μL)	8.26 (4.95-11.08)	2.99 (1.35-5.43)	.326
ANC (/μL)	5282 (2851-8328)	2168 (557-3317)	.004
Platelet (×10 ³ /μL)	138 (59-204)	62 (24-123)	.020
CRP (mg/dL)	3.33 (0.94-6.15)	9.58 (1.99-14.54)	.063
Invasive tests	6 (17.6)	5 (33.3)	.232
Aetiologic diagnosis	18 (52.9)	13 (86.7)	.057
Infectious PI	10 (29.4)	4 (26.7)	.845
Treatment modification based on			.481
Non-invasive tests	17 (50.0)	9 (60.0)	.519
Invasive tests	3 (50.0)	3 (60.0)	.741
Outcome of PI			
PICU admission	6 (17.6)	15 (100.0)	
PICU readmission <7 days	1 (2.9)	6 (40.0)	.007
Days from PI to PICU admission, median (IQR)	1 (0-8)	5 (2-14)	.121

^aMore than grade II acute GVHD and moderate chronic GVHD were included.

^bOverall, 4 of 7 non-survivors and 1 of 3 survivors with hepatic dysfunction had VOD.

outcome among infectious causes, but not among non-infectious causes. Similar to previous studies, we reported a relationship between organ dysfunction and mortality; however, the present study focused on recipients with PIs and the early predictors of mortality, rather than all recipients of HSCT and already critically ill patients. After organ dysfunctions worsen, patients could transfer to the PICU for extracorporeal organ support. Among recipients with

PIs, 21 episodes required PICU admission and only 30% survived. Interestingly, there was no difference in days from the diagnosis to PICU admission for those who survived and those who did not. We may assume that simple organ supportive care with early transfer to the PICU is not enough to inhibit the progression from MODS to mortality. However, no established therapies for organ dysfunction yet exist, although a few molecular targeted therapies have been

TABLE 4 Multivariate analysis of mortality predictors

	P-value	Odds ratio	95% Confidence interval
Hepatic dysfunction	.032	11.145	1.23-101.29
Neutropaenia ^a	.044	10.558	1.07-104.65
Thrombocytopenia ^b	.543	0.452	0.04-5.85

Variables that showed a significant result in the univariate analysis ($P < .05$), noted in Table 3, were included in the multivariate logistic regression: veno-occlusive disease, medications administered (antibiotics, antifungal agent, cytomegalovirus treatment), hepatic dysfunction, neutropaenia, and thrombocytopenia as the representatives of haematologic dysfunction, and the presence of dysfunction in two or more organs. Finally, three of these variables were found to be statically significant using the forward stepwise methods.

^aAbsolute neutrophil count less than 1000/ μ L.

^bPlatelet level less than $100 \times 10^3/\mu$ L.

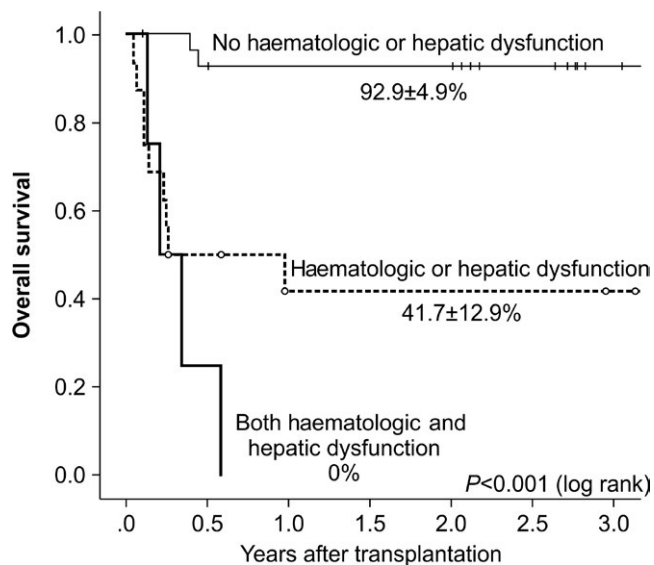


FIGURE 2 Comparison of 3-year overall survival rates for patients with pulmonary complications after hematopoietic stem cell transplantation according to accompanying haematologic and/or hepatic dysfunction

studied.⁴⁸ Therefore, further studies on organ dysfunction treatments are needed to improve outcomes.

The present study has several limitations. First, the study was conducted at a single centre, which may limit the generalizability of our findings to other centres in which close discussions among an experienced oncologist, pulmonologist, and intensivist are not possible. Second, due to the study's retrospective nature, a selection bias may have influenced the results. Third, our patient group was too small to draw powerful conclusions. However, the present study adds to the literature by focusing on the importance of comorbidities and organ dysfunction, which are often neglected in studies focusing on diagnoses. In addition, the adjusted multivariable analysis served to minimize the potential for selection bias. Finally, the lack of the results for pulmonary function tests before and after HSCT

is a limitation of our study. However, about 40% of recipients were children younger than 5 years old, so the lung function tests could not be performed routinely and therefore could not be used as a relative factor of PCs.

In conclusion, hepatic dysfunction and neutropaenia at the time of PI initiation were ascertained to be independent early predictors of mortality. Although additional invasive diagnostic tests led to higher diagnostic yield, aetiologic diagnoses and associated treatment modification did not significantly affect mortality. However, this observation needs to be further evaluated in a multicentre, prospective study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

Yu Hyeon Choi: Participated in study design, data collection, statistical analysis, data interpretation, drafting the article, and approval of the article; Hyung Joo Jeong, Hong Yul An, You Sun Kim, and Eui Jun Lee: Participated in study design, critical revision of the article, and approval of the article; Bongjin Lee and June Dong Park: Participated in data interpretation, drafting the article, critical revision of the article, and approval of the article. Hyoung Jin Kang and Hee Young Shin: Participated in data interpretation and critical revision.

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