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A Study of Pulmonary Infectious and Non-Infectious Complications in a Pediatric Hematopoietic Stem Cell Transplantation (HSCT) Center in Iran

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Abstract

Background: Pulmonary complications are important enough to notice in hematopoietic stem cell transplantation (HSCT). The patients undergoing HSCT might have infectious and non-infectious problems associated with morbidity and mortality. The pulmonary complications of HSCT are well-recognized in adults; however, studies on children are limited, especially in Iran. This study was done to evaluate the infectious and non-infectious pulmonary complications and the corresponding factors in children who underwent HSCT.

Materials and Methods: This retrospective cohort study included the patients who underwent HSCT in Mofid Children's Hospital in Tehran, Iran, during the years 2015 -2021. Overall, 144 medical files were evaluated, out of which 128 had undergone HSCT. The extracted data were about underlying diseases, age at transplant, sex, type of HSCT, donor type, cell source, conditioning regimen, graft versus host disease (GVHD) prophylaxis, infectious and non-infectious pulmonary complications, and associated factors. The data analysis was done by the SPSS software version 26. Chi-square, Fisher exact test and regression were also used for the analysis.

Results: Infectious and non-infectious pulmonary complications were reported in 26 people (20.3%) and 11 people (8.6%), respectively. Positive coronavirus disease 2019 (COVID-19) PCR was detected only in two patients. Infectious complications were significantly lower in patients with neuroblastoma compared to other underlying diseases (2.7% vs. 27.5%, P = 0.002). These complications were significantly more frequent among those with other HSCT complications compared to those without such complications (34.6% vs. 16.7%, P=0.042). Non-infectious pulmonary complications were significantly higher in boys (13.5%) than in girls (1.9%) (P = 0.024).

Conclusion: Due to the high rate of pulmonary infections in bone marrow transplant patients, clear differential diagnosis and diagnostic work are essential.

Keywords: Children, Hematopoietic stem cell transplantation (HSCT), Post-transplant complications , Pulmonary complication

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Introduction

Hematopoietic stem cell transplant (HSCT) has been practiced over the past decades as an increasingly successful option to cure a variety of malignant and nonmalignant disorders in children (1). Annually, 50000 HSCTs are done for the treatment of different types of disorders with a survival rate of more than 80% (2).

Nowadays, the indications for transplant have expanded beyond the malignant disorders such as high-risk acute leukemia, solid tumors, and a wide range of hereditary conditions, including bone

marrow failure syndrome, storage and metabolic disorders, hemoglobinopathies, and immune deficiencies that could be cured with HSCT (3, 4).

The availability of molecular studies (high-resolution molecular studies) better selection of human-leucocyte-antigen (HLA) compatibility between donors and recipients, improved supportive care, use of antibiotic prophylaxis, and better treatment of infections have significantly decreased the mortality and morbidity rates of HSCT and improved the outcome (5, 6).

There are still several complications after HSCT, which is for different reasons such as the conditioning regimen of chemotherapy and/or radiotherapy. These complications are myelosuppression, anemia, thrombocytopenia, mucositi, hemorrhagic cystitis, sinusoidal obstruction syndrome (SOS), acute graft versus host disease (a-GVHD), and bacterial, fungal and viral infections. The most important ones are graft versus host disease (GVHD) and infections. If the presentation of GVHD occurs during 90 days after HSCT, it is considered as acute GVHD; after that, it is deemed as chronic GVHD (7-13). All of these complications can increase mortality and morbidity rates. One of the most important early or late (> 100 days or 3 months after HSCT) complications in HSCT is pulmonary complications. According to the literature, pulmonary complications occur in about 25% of children receiving HSCT. Although early or long-term pulmonary complications after HSCT in adults are well known, studies about such complications are limited in children (14).

Researchers have pointed to non-infectious pulmonary complications in these patients such as idiopathic pneumonia syndrome, obstructive bronchiolitis syndrome, and cryptogenic organizing pneumonia (15). Moreover, infectious etiologies include bacterial, viral and fungal infections, each of which can have considerable mortality if not identified and treated early in the course of infection(16). Considering the importance of diagnosing pulmonary complications in children, this study evaluates the distribution of infectious and non-infectious pulmonary complications and the corresponding factors in pediatric HSCT from 2015 to 2021. The cases were studied in Mofid Children's Hospital of Tehran, Iran.

Materials and Methods

This is a cohort study of the patients who had undergone HSCT at Mofid Children's Hospital of Tehran, Iran, from 2015 to 2021. A total of 144 cases were assessed, and 128 cases were transplanted. The inclusion criteria were age under 18 years and performance of hematopoietic stem cell transplant. The exclusion criteria were the state of being under follow-up for less than one year and missing patient data. The required data were extracted from the patients' files. They were about the underlying disease for transplant, age and sex of the patients, their age at the time of transplantation, type of HSCT (autologous or allogeneic), donor type, source of stem cells bone marrow (BM), peripheral blood (PB), umbilical cord blood (UCB), preparation regimen myeloablative conditioning (MAC) vs reduced intensity (RIC), GVHD-prophylaxis, and infectious and non-infectious pulmonary complications. A pulmonary infection referred to any viral, bacterial or fungal infection. The survival rate showed the percentage of the patients who were alive one year after transplantation.

In order to assess the pulmonary complications in those who underwent HSCT, a sample size of 120 patients was determined based on the data from a previous study and a certain formula. The statistical test power was set at 80% with a 95% level of confidence.

$$n = \frac{(Z_{\alpha/2} + Z_{\beta}) + (\sigma_1 + \sigma_2)^2}{(\mu_1 - \mu_2)^2}$$

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The ethics committee of Shahid Beheshti Medical University approved the study (IR.SBMU.MSP.REC.1400.254).

Statistical analysis

The data analysis was done by the SPSS software version 26. To describe the data, frequency percentages, means and standard deviations were reported. Kolmogorov-Smirnov and Shapiro-Wilk tests served to determine the normality distribution. Chi-square and univariate and multivariate logistic regression were also used for the data analysis. In all the analyses, $P < 0.05$ was considered as the level of significance.

Results

The characteristics of 128 patients were studied. Of them, 74 (57.8%) were male, and 54 (42.2%) were female. Their mean age of transplantation was 6.11 ± 3.99 years. Totally, 84 (65.6%) of the patients received allogeneic HSCT, and 44 (34.4%) received autologous HSCT. In 106 (82.8%) cases, the cell source was peripheral blood (PB), bone marrow in 13 (10.2%), and umbilical cord blood (UCB) in 9 (7%) patients. The underlying diseases causing transplantation in most patients were malignant disorders including neuroblastoma in 38 (29.7%) cases followed by leukemia in 32 (25%) cases. AML (18 people, 14.1%), ALL (13 people, 10.2%) and juvenile myelomonocytic leukaemia (JMML) (1 patient, 0.8%) were in the group of leukemia. In the group of non-malignant disorders, primary immunodeficiency disorders (PID) were found in 15 patients (11.7%) including 5 hemophagocytic lymphohistiocytosis (HLH) cases (3.9%), 3 severe combined immunodeficiency (SCID) cases (2.3%), 2 chronic granulomatous disease (CGD) cases (1.6%), 1 leukocyte adhesion deficiency (LAD) case (0.8%), and other rare primary immunodeficiencies (interleukin 10 deficiency in 1 child, 0.8%). The next group was for bone marrow failure disorders in 17 (13.3%) patients, including fanconi anemia (7 children, 5.5%), aplastic anemia (6 children, 4.7%), dyskeratosis congenita (3 children, 2.3%), and pure red blood cell aplasia (1 patient, 0.8%). In the group of lymphomas, there were eight patients including hodgkin's lymphoma (5 patients, 3.9%), non-Hodgkin's lymphoma (B-Cell) (2 patients, 1.6%), and T-cell lymphoma (1 child, 0.8%). Finally, in the metabolic disorder group, there were seven children (5.5%) four of whom (3.1%) had adrenoleukodystrophy (ALD), two (1.6%) had metachromatic leukodystrophy (MLD), and one (0.8%) suffered from mucopolysacharidois (MPS). They all received HSCT. Regarding the preparation regimen, 118 (92.2%) of the patients took a myeloablative conditioning (MAC) regimen, and reduced intensity regimen was applied to 10 cases (7.8%). GVHD prophylaxis was used based on the underlying disease and the type of HSCT. In this regard, 39 patients (46.4%) received cyclosporine plus methotrexate, 37 (44%) received cyclosporine plus mycophenolate mofetil, 4 (4.8%) took cyclosporine plus methylprednisolone, and 4 (4.8%) were given cyclosporine plus mycophenolate mofetil plus cyclophosphamide (for haploidentical HSCT). In this study, 31 patients (24.2%) had pulmonary complications. Also, a total of 26 patients (20.3%) had non-pulmonary complications. Infectious pulmonary complications occurred in 26 patients (20.3%). Of the infections, 22 cases were viral, 6 were fungal, and 3 were bacterial. Among the fungal cases, only 3 were definite cases, and the other 3 cases were probable ones (based on the clinical evidence including prolonged fever, imaging evidence, and galactomannan evaluation). Moreover, 22 patients (17.2%) had one infectious pathogen, 3 patients (2.3%) had two infectious pathogens, and

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1 (0.8%) had three infectious pathogens. Positive COVID-19 PCR was detected only in two patients. One patient was a 13-year-old boy with diagnosed AML. He improved by receiving allogenic HSCT from an HLA-matched sibling donor (MSD). The other patient was a 10-year-old boy with diagnosed ALL. He received allogenic HSCT from MSD and had refractory blood, CSF gram positive bacterial infection (enterococous), and, at the same time, positive COVID-19 PCR. He had no response to the treatment and died. Non-infectious pulmonary complications were observed in 11 patients (8.6%), including six cases of pulmonary hemorrhage, five cases of respiratory failure (with three cases of ARDS), two cases of Brochiolitis oblitraan (BO), two cases of pulmonary edema, one case of idiopathic pulmonary fibrosis (IPF), and one case of mild obstruction defect. Six (4.7%) patients had one non-infectious cause, four (3.1%) had two non-infectious causes, and one patient (0.08%) had three non-infectious complications. The prevalence of pulmonary complications and survival based on sex, age, and underlying diseases is reported in Table I. The prevalence of pulmonary complications and survival based on the type of HSCT, cell source, conditioning regimen, and regimen for the prevention of GVHD is reported in Table II.

Pulmonary infectious complications in the patients with other types of transplant complications were significantly higher than those in the patients without other complications (34.6% vs. 16.7%, P = 0.042). The survival rate in these patients was significantly lower (34.6% vs. 77.5%, P < 0.001). However, there was no significant difference between the patients with other transplant complications and the patients without these complications in terms of non-infectious pulmonary complications (P = 0.232). The survival of the patients in this study was 68.8% (i.e., 88 patients). The highest mortality rate belonged to the patients with neuroblastoma (14 people, 10.9%). Next to that, leukemia (9 patinets, 7%), primary immunodeficiency (8 patinets, 6.3%), metabolic diseases (4 patinets, 3.1%), and bone marrow failure (2 patinets, 1.6%) were the main causes of mortality. No mortality was observed among the children diagnosed with lymphoma.

Logistic regression was conducted to evaluate the factors for pulmonary complications and survival. The results are reported in Table III.

According to the univariate analysis, the type of HSCT, the underlying disease, and the type of donor were significantly related to the occurrence of pulmonary complications in the children receiving HSCT. Based on the adjusted model, however, none of the factors had a significant relationship with the occurrence of pulmonary complications. As in Table IV, although the univariate analysis showed that the type of HSCT, the underlying disease, the type of transplant donor, other complications, and non-infectious pulmonary complications had significant relationships with the occurrence of pulmonary complications in the children receiving HSCT, the adjusted model proved no such relationships with infectious pulmonary complications. According to Table V, the univariate analysis provided evidence for the significant relationship of other complications and pulmonary complications with survival rate in the children receiving HSCT. Based on the multivariate analysis, even after adjustment in terms of cell source, preparation regimen and pulmonary complications, the other complications had a negative and significant relationship with survival.

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These complications reduced the chance of survival by 83% (aOR = 0.17, with a 95% confidence interval in the range of 0.06 to 0.45, P < 0.001).

Table I: Prevalence of infectious and non-infectious pulmonary complications and survival based on sex, age, and underlying diseases

Variables		Sex, N (%)		P-value*
		Male (n = 74)	Female (n = 54)	
Infectious pulmonary complications	Yes	17 (23.0)	9 (16.7)	0.381
	No	57 (77.0)	45 (83.3)	
Non-infectious pulmonary complications	Yes	10 (13.5)	1 (1.9)	0.024
	No	64 (86.5)	53 (98.1)	
Survival	Yes	53 (71.6)	35 (64.8)	0.412
	No	21 (28.4)	19 (35.2)	
Variables		**Transplant age, N (%)**		**P-value**
		≤ 5 years (n = 63)	> 5 years (n = 65)	
Infectious pulmonary complications	Yes	12 (19.0)	14 (21.5)	0.726
	No	51 (81.0)	51 (78.5)	
Non-infectious pulmonary complications	Yes	4 (6.3)	7 (10.8)	0.372
	No	59 (93.7)	58 (89.2)	
Survival	Yes	42 (66.7)	46 (70.8)	0.617
	No	21 (33.3)	19 (29.2)	
Variables		**Underlying disease, N (%)**		**P-value**
		Neuroblastoma (n = 37)	Others (n = 91)	
Infectious pulmonary complications	Yes	1 (2.7)	25 (27.5)	0.002
	No	36 (97.3)	66 (72.5)	
Non-infectious pulmonary complications	Yes	1 (2.7)	10 (11.0)	0.175
	No	36 (97.3)	81 (89.0)	
Survival	Yes	23 (62.2)	65 (71.4)	0.305
	No	14 (37.8)	26 (28.6)	
*** Chi-square test**				

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Table II: Prevalence of pulmonary complications and survival based on the type of HSCT, cell source, conditioning regimen, and regimen for the prevention of GVHD

Variables		HSCT type, N (%)		P-value*
		Allogenic (n = 84)	Autologous (n = 44)	
Infectious pulmonary complications	Yes	25 (29.8)	1 (2.3)	< 0.001
	No	59 (70.2)	43 (97.7)	
Non-infectious pulmonary complications	Yes	10 (11.9)	1 (2.3)	0.096
	No	74 (88.1)	43 (97.7)	
Survival	Yes	57 (67.9)	31 (70.5)	0.763
	No	27 (32.1)	13 (29.5)	
Variables		**Conditioning regimen, N (%)**		**P-value**
		Myeloablative (n = 118)	Reduced intensity (n=10)	
Infectious pulmonary complications	Yes	26 (22.0)	0 (0.0)	0.212
	No	92 (78.0)	10 (100.0)	
Non-infectious pulmonary complications	Yes	10 (8.5)	1 (10.0)	0.991
	No	108 (91.5)	9 (90.0)	
Survival	Yes	83 (70.3)	5 (50.0)	0.284
	No	35 (29.7)	5 (50.0)	
Variables		**Cell source, N (%)**		**P-value**
		Peripheral blood (n = 106)	Bone marrow (n = 13)	Cord blood (n=9)
Infectious complications	Yes	23 (21.7)	2 (15.4)	1 (11.1)	0.751
	No	83 (78.3)	11 (84.6)	8 (88.9)	
Non-infectious complications	Yes	11 (10.4)	0 (0.0)	0 (0.0)	0.554
	No	95 (89.6)	13 (100.0)	9 (100.0)	
Survival	Yes	70 (66.0)	12 (92.3)	6 (66.7)	0.141
	No	36 (34.0)	1 (7.7)	3 (33.3)	
Variables		**GVHD regimen, N (%)**			**P-value**
		Cyclo+MTX	Cyclo+MMF (n = 37)	Others (n = 8)	
Infectious complications	Yes	14(35.9)	9 (24.3)	2 (25.0)	0.519
	No	25(64.1)	28 (75.7)	6 (75.0)	
Non-infectious complications	Yes	5 (12.8)	5 (13.5)	0 (0.0)	0.786

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	No	34(87.2)	32 (86.5)	8 (100.0)	
Survival	Yes	29(74.4)	23 (62.2)	5 (62.5)	0.494
	No	10(25.6)	14 (37.8)	3 (37.5)	
*** Chi-square test**					

Table III: Evaluation of the factors related to pulmonary complications (infectious or non-infectious) in children undergoing transplantation

Independent variables		cOR (95% CI)	P-value	aOR (95% CI)	P-value*
Sex	Male	1.74 (0.74; 4.09)	0.201	-	-
	Female	1.00	-	-	-
Transplant age (years)		1.08 (0.98; 1.19)	0.142	1.11 (0.99; 1.24)	0.087
Underlying disease	Neuroblastoma	1.00	-	1.00	-
	Others	8.19 (1.84; 36.38)	0.006	1.34 (0.15; 11.86)	0.792
HSCT type	Allogenic	11.07 (2.50; 49.04)	0.002	18.71 (0.58; 606.41)	0.099
	Autologous	1.00	-	1.00	-
Donor type	Autologous	1.00	-	1.00	-
	MSD	13.73 (2.93; 64.35)	0.001	0.58 (0.03; 10.53)	0.715
	MRD	15.75 (2.99; 82.92)	0.001	0.70 (0.04; 13.45)	0.813
	Unrelated cord blood	3.50 (0.27; 44.75)	0.335	0.17 (0.01; 5.84)	0.327
	MUR	2.10 (0.17; 25.52)	0.560	0.08 (0.00; 2.47)	0.146
	Haploidentical	21.00 (0.93; 472.59)	0.055	-	-
Cell source	Bone marrow	1.00	-	-	-
	Peripheral blood	1.97 (0.41; 9.46)	0.395	-	-
	Cord blood	0.69 (0.05; 8.96)	0.775	-	-
Conditioning regimen	Myeloablative	3.07 (0.37; 25.24)	0.297	-	-
	Reduced intensity	1.00	-	-	-
GVHD regimen	Cyclo+MTX	1.00	-	-	-
	Cyclo+MMF	0.61 (0.24; 1.57)	0.305	-	-
	Others	0.48 (0.09; 2.68)	0.403	-	-
Other complications	No	1.00	-	1.00	-
	Yes	2.41 (0.96; 6.08)	0.062	1.35 (0.48; 3.84)	0.570
Abbreviations: cOR (crude odds ratio), CI (confidence interval), aOR (adjusted odds ratio)					
*** Univariate and multivariate logistic regression**					

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Table IV: Determination of the factors associated with survival in the transplanted children

Independent variables		cOR (95% CI)	P-value	aOR (95% CI)	P-value*
Sex	Male	1.37 (0.65; 2.91)	0.413	-	-
	Female	1.00	-	-	-
Transplant age (years)		1.06 (0.96; 1.16)	0.281	-	-
Underlying disease	Neuroblastoma	1.00	-	-	-
	Others	1.52 (0.68; 3.40)	0.307	-	-
HSCT type	Allogenic	1.00	-	-	-
	Autologous	1.13 (0.51; 2.50)	0.763	-	-
Donor type	Autologous	1.00	-	-	-
	MSD	0.97 (0.39; 2.42)	0.944	-	-
	MRD	0.84 (0.28; 2.56)	0.757	-	-
	Unrelated cord blood	1.05 (0.18; 6.11)	0.958	-	-
	MUR	0.73 (0.18; 2.94)	0.662	-	-
	Haploidentical	0.42 (0.02; 7.22)	0.550	-	-
Cell source	Bone marrow	1.00	-	1.00	-
	Peripheral blood	0.16 (0.02; 1.30)	0.086	0.23 (0.03; 1.92)	0.174
	Cord blood	0.17 (0.01; 1.96)	0.154	0.31 (0.02; 4.33)	0.387
Conditioning regimen	Myeloablative	2.37 (0.65; 8.71)	0.193	2.90 (0.71; 11.86)	0.139
	Reduced intensity	1.00	-	1.00	-
GVHD regimen	Cyclo+MTX	1.00	-	-	-
	Cyclo+MMF	0.57 (0.21; 1.51)	0.255	-	-
	Others	0.58 (0.12; 2.85)	0.498	-	-
Other complications	Yes	0.15 (0.06; 0.39)	<0.001	0.17 (0.06; 0.45)	-
	No	1.00	-	1.00	< 0.001
Pulmonary complications	No	0.37 (0.16; 0.86)	0.020	0.43 (0.17; 1.09)	-
	Yes	1.00	-	1.00	0.076
Abbreviations: cOR (crude odds ratio), CI (confidence interval), aOR (adjusted odds ratio)					
*** Univariate and multivariate logistic regression**					

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Table V: Assessment of the factors associated with the survival rate in the patients

Independent variables		cOR (95% CI)	P-value	aOR (95% CI)	P-value*
Sex	Male	1.37 (0.65; 2.91)	0.413	-	-
	Female	1.00	-	-	-
Transplant age (years)		1.06 (0.96; 1.16)	0.281	-	-
Underlying disease	Neuroblastoma	1.00	-	-	-
	Others	1.52 (0.68; 3.40)	0.307	-	-
HSCT type	Allogenic	1.00	-	-	-
	Autologous	1.13 (0.51; 2.50)	0.763	-	-
Donor type	Autologous	1.00	-	-	-
	MSD	0.97 (0.39; 2.42)	0.944	-	-
	MRD	0.84 (0.28; 2.56)	0.757	-	-
	Unrelated cord blood	1.05 (0.18; 6.11)	0.958	-	-
	MUR	0.73 (0.18; 2.94)	0.662	-	-
	Haploidentical	0.42 (0.02; 7.22)	0.550	-	-
Cell source	Bone marrow	1.00	-	1.00	-
	Peripheral blood	0.16 (0.02; 1.30)	0.086	0.23 (0.03; 1.92)	0.174
	Cord blood	0.17 (0.01; 1.96)	0.154	0.31 (0.02; 4.33)	0.387
Conditioning regimen	Myeloablative	2.37 (0.65; 8.71)	0.193	2.90 (0.71; 11.86)	0.139
	Reduced intensity	1.00	-	1.00	-
GVHD regimen	Cyclo+MTX	1.00	-	-	-
	Cyclo+MMF	0.57 (0.21; 1.51)	0.255	-	-
	Others	0.58 (0.12; 2.85)	0.498	-	-
Other complications	Yes	0.15 (0.06; 0.39)	<0.001	0.17 (0.06; 0.45)	-
	No	1.00	-	1.00	< 0.001
Pulmonary complications	Yes	0.37 (0.16; 0.86)	0.020	0.43 (0.17; 1.09)	-
	No	1.00	-	1.00	0.076

Abbreviations: cOR (crude odds ratio), CI (confidence interval), aOR (adjusted odds ratio)

*** Univariate and multivariate logistic regression**

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Discussion

During the last decades, HSCT has been used for different types of malignant and non-malignant, hematological and non-hematological, and hereditary and acquired diseases in children. Different types of HSCT are available, and they may directly affect clinical outcomes. However, treatment outcome is limited by complications secondary to immunosuppression and treatment-related toxicity. One of the most important complications is pulmonary complication, which may appear as infectious or non-infectious events. According to different studies, pulmonary complications occur in about 40-60% of patients receiving HSCT. They might occur shortly or long after HSCT. Infectious complications are more common in allogeneic transplants due to GVHD and immunosuppressive drugs, and the lung is a particular target organ post-transplant for infectious diseases. They might be viral, bacterial or fungal infections. Until recently, pulmonary complications were largely attributed to infectious causes, but there is now a relative decrease in infection with the use of a broad range of antimicrobial agents for prophylaxis and treatment. Despite the recent improvement of the results of using HSCT, there are still several reasons for morbidity and mortality in pediatric HSCT. The important reasons include underlying diseases, various infectious pathogens, and GVHD that might be acute or chronic (13). In the present study, which was conducted on 128 children undergoing HSCT, pulmonary complications occurred in about 25% of the patients. This is almost consistent with the percentages reported in previous studies (17). Chong-Silva et al. (18) reported pulmonary complications in 27.3% of the patients after HSCT, but they only examined patients under 14 years of age. The rate of pulmonary complications in the study of Çıkı et al. (14) was 36.4%.

Various factors may affect the incidence of pulmonary complications, including underlying diseases, preparation regimen, GVHD prevention regimen, type of the transplant donor, and source of the stem cells for transplantation, all of which were investigated in this study. The difference in these factors can account for the higher rate of pulmonary complications in the study by Çıkı et al. (14). The rate of pulmonary complications in the children studied by Dogulu et al. (19) was 46.7%. In this study, advanced age at diagnosis and impaired renal function before transplantation were the risk factors for pulmonary complications, but the present study did not identify any factor as a predictor of pulmonary complications (infectious and non-infectious). Fazekas et al. (20) reported pulmonary complications in 35% of the children receiving allogeneic HSCT. It seems that a major reason for the difference between the results of that study and the present study was the reporting of just allogeneic HSCT recipients, while both allogeneic and autologous types of HSCT were included in the present study. As for this study, it is to be mentioned that transplantation in Mofid Children's Hospital was started with a group of autologous HSCTs in the first year of its activity; thus, neuroblastoma patients were high in number for HSCT in this study. This may have affected the results of the study. Also, the high risk of disease recurrence in the neuroblastoma patients, despite using various treatments such as chemotherapy, radiotherapy, autologous transplantation and maintenance therapy, was about 50%, and it was about 70% with immunotherapy (Anti Gd2-Dinutuximab). In Mofid hospital, there was no access to dinutuximab (21). The results of the present study showed that infectious and non-infectious pulmonary complications

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occurred in 20.3% and 8.6% of the patients, respectively. Çıkı et al. (14) reported infectious pulmonary complications in 34.1% and non-infectious pulmonary complications in 24.4% of their patients. Also, Bergeron et al. (22) reported the late cumulative incidence of non-infectious complications in 19.8% of their patients after allogeneic HSCT. It seems that the functional status of the lungs before transplantation or even shortly after transplantation is a predictor of non-infectious pulmonary complications (22). Dogulu et al. (19) had different findings. In their study, there was no statistically significant difference between the patients with and without pulmonary complications in terms of spirometry results and the diffusing capacity of the lungs for carbon monoxide (DLCO) before HSCT. Similarly, as found by Fazekas et al. (20), the non-normal results of pulmonary function tests before transplantation were not significantly associated with the risk of fatal pulmonary complications. In the present study, based on an evaluation protocol, all of the patients were examined by pulmonary specialists before transplantation, and lung function tests were performed for the patients based on their age. The results were normal for all. In the study by Dogulu et al. (19), the rate of pulmonary infectious complications was 68.7%. As they found, like in the majority of studies, prophylactic management for infectious diseases in patients receiving HSCT transplants (including acyclovir for HSV and CMV infections, fluconazole or voriconazole for fungal infections, and cotrimoxazole for pneumocystis jirovecii infection) is an important factor that reduces the incidence of infectious complications in both autologous and allogeneic transplants based on the respective protocols. In a study on autologous HSCT cases, the etiology of pulmonary complications was found to be 13.9% for infectious and 10.2% for non-infectious complications (17); the percentage of non-infectious complications was close to that in the present study, considering both types of autologous and allogeneic transplantation. It should be noted that, in the present study, the most common cause of infectious pulmonary complications was viral infection. However, according to previous studies, bacterial pneumonia is the most common infectious complication in all phases, and its incidence reaches 45% (23, 24). In this study, based on the time of the COVID-19 pandemic, there were just two patients with positive COVID-19 PCR in the leukemia group, one of whom improved and is currently in complete remission 3.5 years after HSCT. The other one died duo to persistent bacterial gram positive infection (enterococous) as well as positive COVID-19 PCR at the same time. In the present study, there was no significant difference in terms of infectious and non-infectious pulmonary complications between the patients receiving a conditioning regimen including MAC compared to the patients receiving an RIC regimen. These two groups of patients were similar in terms of survival. On the contrary, in the research by Çıkı et al. (14), the number of the patients receiving a MAC regimen for conditioning was significantly higher in the group without pulmonary complications than in the group with pulmonary complications. In this research, 68.8% of the patients survived. Several factors play a role in the morbidity and mortality of transplant patients, including underlying diseases, infectious agents, and GVHD. Also, the improvement of care intervention plays an important role in the survival of patients and transplant results. A major factor in determining the prognosis of patients is the occurrence of infectious complications and GVHD. In their study in France, Brissot et al. (25) assessed the results of

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transplantation of 250 children from 1983 to 2010. They also compared the 5-year periods of the patients' survival from 2000 to 2010 and from 1983 to 1990. The survival rate from 2000 to 2010 was 64%, and the mortality rate in various fields other than recurrence was 27%. In a retrospective cohort study in Brazil from 2010 to 2017, Jardim et al. (26) examined a total of 292 transplant patients. The mortality rate was reported to be 5.8% within 100 days, which was clearly higher in the cord blood transplant recipient group. Infectious complications were common and included viral infection (75.3%), bacterial infection (27%), and fungal infection (12%). In another study by Chong-Silva et al. (18), the mortality rate was reported in 19.3% of the patients. Zidan et al. (27) reviewed a low number of allogeneic HSCT patients and reported a mortality rate of 5%. In the present study, the existence of other complications had a negative and significant relationship with the survival of the patients receiving HSCT, which may account for the differences among the figures reported in different studies.

This study is not without limitations. Firstly, it is of a retrospective nature. Secondly, it is conducted on a relatively small sample size, which limits the generalizability of the findings.

Conclusion

Based on the results of this study, almost a quarter of the patients underwent HSCT had pulmonary complications. There was a significant relationship between the non-infectious pulmonary complications of HSCT and gender as well as infectious pulmonary complications and underlying diseases. There were also associations with other transplant complications.

The existence of other complications had a negative and significant correlation with survival in the patients receiving HSCT.

Ethical considerations

The ethics committee of Shahid Beheshti Medical University approved the study (IR.SBMU.MSP.REC.1400.254).

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Authors' contributions

SA.T, M.Gh and B.Sh conceived and planned the study. SA.T, M.Gh and B.Sh contributed to sample preparation. SA.T and M.Gh and contributed to the analysis and interpretation of the results. SA.T and M.Gh wrote the manuscript. All the authors provided critical feedbacks and helped to shape the research, the analyses involved, and the manuscript.

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Conflict of interest

There is no conflict of interests to declare.

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