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HOW DOES MYELOID OR LYMPHOID ORIGIN OF HEMATOLOGIC MALIGNANCY AFFECT PULMONARY FUNCTION, MUSCLE STRENGTH, EXERCISE CAPACITY, AND QUALITY OF LIFE?

ORIGINAL ARTICLE

ABSTRACT

Purpose: Although recipients' muscle strength, exercise capacity and quality of life (QOL) may deteriorate during allogeneic hematopoietic stem cell transplantation (AHSCT), impacts on pulmonary function, muscle strength, exercise capacity, and QOL are still unknown in recipients based on immunophenotypes. Therefore, this study aimed to investigate retrospectively physical impairments and QOL between recipients with myeloid and lymphoid malignancies.

Methods: Pulmonary function (FEV_1, FVC, PEF, FEV_1/FVC, and $FEF_{25-75\%}$), quadriceps and respiratory muscle strength, exercise capacity (incremental shuttle walk test, ISWT), and QOL of 25 recipients with myeloid (42.76±14.72 years) and 22 recipients with lymphoid (37.27±14.13 years) hematologic malignancies (>100 days post-AHSCT status) were analyzed retrospectively.

Results: Age, gender, FEV_1, FVC, PEF, quadriceps strength, QOL scores, and ISWT distance (lymphoid: 637.27±211.1 m, myeloid: 704±211.6 m, difference: 66.73 m) were similar between the groups (p>0.05). Lymphoid group's FEV_1/FVC and $FEF_{25-75\%}$ values were statistically higher, and the percentage of ISWT distance (effect size d=0.97, power (1-β)=0.89), maximum inspiratory pressure (lymphoid: 106.64±23.99 cmH_2O, myeloid: 121.88±24.4 cmH_2O, difference: 15.24 cmH_2O) and maximum expiratory pressure (lymphoid: 122.55±38.29 cmH_2O, myeloid: 146.72±33.06 cmH_2O, difference: 24.18 cmH_2O) were significantly lower than the myeloid group (p<0.05).

Conclusion: All recipients had common debilitating problems on exercise capacity, lower extremity strength, and QOL. However, recipients with lymphoid type disorder had more reduced respiratory muscle strength and exercise capacity. Small airway obstruction was more commonly observed respiratory dysfunction in recipients with myeloid type disorder. Modifying and adjusting contents of rehabilitation programs according to immunophenotype of hematologic malignancy should be considered in further study.

Key Words: Exercise Test; Hematologic Neoplasms; Hematopoietic Stem Cell Transplantation; Muscle Strength; Quality of Life.

HEMATOLOJİK MALİGNİTENİN MİYELOİD VEYA LENFOİD KÖKENİ SOLUNUM FONKSİYONU, KAS KUVVETİ, EGZERSİZ KAPASİTESİ VE YAŞAM KALİTESİNİ NASIL ETKİLER?

ARAŞTIRMA MAKALESİ

ÖZ

Amaç: Allojeneik hematopoetik kök hücre transplantasyonu (AHKHT) boyunca alıcıların kas kuvveti, egzersiz kapasitesi ve yaşam kalitesi kötüleşmesine rağmen, alıcılarda immunofenotipik özelliklere göre solunum fonksiyonları, kas kuvveti, egzersiz kapasitesi ve yaşam kalitesi üzerine etkiler halen bilinmemektedir. Bu yüzden, bu çalışmada miyeloid ve lenfoid maliniteli alıcılar arasında fiziksel bozuklukların ve yaşam kalitesinin retrospektif olarak araştırılması amaçlandı.

Yöntem: Yirmi beş miyeloid (42,76±14,72 yıl) ve 22 lenfoid (37,27±14,13 yıl) hematolojik maliniteli alıcılarının (AHKHT sonrası durumu >100 gün) solunum fonksiyonları (FEV_1, FVC, PEF, FEV_1/FVC ve $FEF_{\%25-75}$), quadriceps kuvveti ve solunum kas kuvveti, egzersiz kapasitesi (artan hızda mekik yürüme testi, AHMYT) ve yaşam kalitesi retrospektif olarak analiz edildi.

Sonuçlar: Yaş, cinsiyet, FEV_1, FVC, PEF, quadriseps kas kuvveti, yaşam kalitesi puanları ve AHMYT mesafesi (lenfoid: 637,27±211,10 m, miyeloid: 704,00±211,60 m, fark: 66,73 m) gruplar arasında benzerdi (p>0,05). Miyeloid gruba göre lenfoid grubun FEV_1/FVC ve $FEF_{\%25-75}$ değerleri istatistiksel olarak daha yüksekti (p<0,05), ve AHMYT mesafesi yüzdesi (etki büyüklüğü d=0.97, güç (1-β)=0.89), maksimum inspiratuar basınç (lenfoid: 106,64±23,99 cmH_2O, miyeloid: 121,88±24,40 cmH_2O, fark: 15,24 cmH_2O) ve maksimum ekspiratuar basınç (lenfoid: 122,55±38,29 cmH_2O, miyeloid: 146,72±33,06 cmH_2O, fark: 24,18 cmH_2O) ise, anlamlı olarak daha düşüktü (p<0,05).

Tartışma: Tüm alıcılar egzersiz kapasitesi, alt ekstremite kas kuvveti ve yaşam kalitesi konusunda benzer zayıflatıcı problemlere sahipti. Ancak, lenfoid tip bozukluğu olan alıcılar daha düşük solunum kas kuvveti ve egzersiz kapasitesine sahiptiler. Küçük havayolu obstrüksiyonuysa, miyeloid tip bozukluğu olan alıcılarda daha yaygın olarak gözlenir. Rehabilitasyon programı içeriklerinin hematolojik malinitenin immunofenotipine tipine göre düzenlenmesi ve ayarlanması yaklaşımı üzerinde durulması gereken bir konudur.

Anahtar Kelimeler: Egzersiz Testi; Hematolojik Neoplazmlar; Hematopoietik Kök Hücre Transplantasyonu; Kas Kuvveti; Yaşam Kalitesi.

INTRODUCTION

Hematologic malignancies affecting the blood, bone marrow, and lymph nodes comprise either myeloid or lymphoid blood stem cells of origin (1,2). While a lymphoid stem cell differentiates to a lymphocyte, a myeloid stem cell becomes one of the red blood cells, white blood cells or platelets. Defects in myeloid stem cells result in acute and chronic myeloid neoplasms, myelodysplastic syndromes or myeloproliferative diseases, whereas defects in lymphoid stem cells result in lymphoma, acute or chronic lymphocytic leukemia or myeloma (1,2). However, most of these hematologic malignancies are characterized by higher rates of morbidity and mortality because of both nature and side effects of various treatments including chemotherapy with multiple agents, corticosteroids, and hematopoietic stem cell transplantation (HSCT) (1,2). Especially after allogeneic HSCT, recipients experience higher rates of impairments in pulmonary function, respiratory and peripheral muscle strength, exercise capacity and quality of life scores which make their lives difficult in terms of actively trying to return to their life (3,4). In addition, these impairments may lead to pulmonary complications (5) which HSCT process along with physical complications, may be even fatal for allogeneic recipients. Although each hematologic disease has different negative impacts on various body systems or organs after HSCT (1), little attention has been paid to the comparative investigation of impacts of myeloid and lymphoid hematologic malignancies on pulmonary functions, muscle strength, exercise capacity, and quality of life in allogeneic HSCT recipients. There is no study investigating the differentiation of physical impairments in recipients based on blood cell type to the best of our knowledge. Therefore, the present study aimed to investigate retrospectively physical impairments between recipients with hematologic malignancies according to the cell of origin.

METHODS

Study Design

A retrospective study was conducted at Gazi University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Ankara, Turkey. The data were anonymized. Gazi University Ethics Committee approved the retrospective study (Number: 2018-18). The study was followed by the principles of the Declaration of Helsinki. Written informed consent forms were not necessary to be obtained from participants since the data were anonymized in this retrospective study.

Participants

The data of the patients who were referred for participation in the rehabilitation program as an outpatient from the Bone Marrow Transplantation Unit between March 2012 and December 2016 were retrospectively analyzed. Fifty-seven patients diagnosed with hematologic malignancy were recipients who underwent allogeneic HSCT. Ten recipients were excluded from the analysis due to the reasons including older age (>65 years) (n=2), orthopedic problem (n=5) and cutaneous graft-versus-host disease (GvHD) (n=3), which limited them to walk. Of 47 allogeneic HSCT recipients 25 had myeloid and 22 lymphoid type disorder. The diagnostic distribution of recipients in the groups was as follows: the myeloid group included 14 (56%) acute myeloid leukemia, eight (32%) myelodysplastic syndrome, and three (12%) chronic myeloid leukemia while the lymphoid group included 16 (72.7%) acute lymphoblastic leukemia, two (9.1%) Non-Hodgkin lymphoma, and four (18.2%) multiple myeloma.

Inclusion criteria for the analyses were 18-65 years of age, being an allogeneic HSCT recipient who was at minimum 100 days status post HSCT and receiving optimal standard medical therapy including immunosuppressive agents, antibiotics, supplements, and other drugs. Exclusion criteria were cognitive disorders, orthopedic or neurological disease with a potential to affect the assessment of exercise capacity, acute hemorrhage, comorbidities such as asthma, chronic obstructive pulmonary disease, acute respiratory or other infections, visual impairments, and mucositis that may limit measurements. The reason for the inclusion of these recipients at a minimum 100 days status after HSCT was the period beginning from day 100 is the intermediate/late recovery phase of allogeneic-HSCT survivors (6). Furthermore, as physical functioning rapidly decreases immediately after HSCT, early moderate impairments frequently

return to pre-HSCT levels after 100 days in HSCT survivors (6).

The data related to the patient summary of transplantation, performance status before HSCT and total blood counts including hemoglobin, platelet, white blood cell, blood glucose level, albumin, and total protein were obtained from hospital records. Performance status for cancer patients, which was evaluated based on the Eastern Cooperative Oncology Group (ECOG) (7) and Karnofsky Performance Status (8), were recorded.

Exercise Capacity

Incremental shuttle walk test (ISWT) distance was recorded as a measure of maximal exercise capacity and also expressed as a percentage of predicted values (9). Vital signs, including heart rate, oxygen saturation, blood pressure, respiratory rate, as well as dyspnea and fatigue perceptions measured before and after the ISWT were also recorded. The minimal clinically important difference (MCID) for ISWT, 47.5 m, was used (10).

Pulmonary Function Test

Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow rate (PEF), and forced expiratory flow at 25-75% ($FEF_{25-75\%}$) were obtained from the records. Pulmonary function test had been performed using a spirometer (Vmax 220 SensorMedics Corporation, Yorba Linda, CA, USA) concerning American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (11). The values of FEV_1, FVC, FEV_1/FVC, PEF, and $FEF_{25-75\%}$ expressed as percentages of expected values (12) were used for the analysis.

Respiratory Muscle Strength

Inspiratory or expiratory muscle strength was recorded as the measurements of maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) which had been performed using a portable mouth pressure device (Micro Medical MicroRPM, England, UK) according to guidelines of ATS/ERS (13). The highest measured values for MIP and the MEP were recorded. In addition, reference values were used to interpret results (14). The guidelines have indicated that a MIP with a lower limit than 80 cmH_2O also demonstrates clinically significant inspiratory muscle weakness (13). Furthermore, values of MEP with lower limits of 160 cmH_2O for men and 120 cmH_2O for women suggest expiratory muscle weakness (15). The MCID for MIP, 13cmH_2O, was also used (16).

Quadriceps Strength

Quadriceps femoris muscle strength, which was measured as the highest value of both sides, a hand-held dynamometer (JTECH Commander, Salt Lake City, USA) was used. Reference values were used to state the percentages of predicted values (17). The MCID for quadriceps femoris muscle strength, 17.2 N, was used to interpret the mean difference (18).

Quality of Life

The quality of life data was obtained using the Turkish version of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 version 3.0 (EORTC QLQ-C30) (19), and the permission to use the questionnaire was previously obtained. This self-administered questionnaire incorporates five functional subscales, including social functioning subscale, three symptom subscales, including fatigue subscale and global health status as well as several single items. All item scores are transformed into a percent (0–100). Higher values represent a higher functional/healthy level in functional subscales, a higher quality of life level in global health status, and an increased presence of symptoms in symptom subscales (20). To interpret the significant change in the quality of life scores, investigators use the statement of Osoba et al. (21). If the value of each subscale respectively changes about 5-10%, 11-20%, and >20%, it shows “a little,” “moderate,” and “very much” change in subscales of EORTC QLQ-C30 (21).

Statistical Analysis

Windows-based SPSS 15.0 statistical analysis program was selected to perform statistical analysis (SPSS Inc., Chicago, Illinois, USA). Visual (histograms, probability plots) and analytical methods (Shapiro-Wilk’s test) were used to determine the presence of normally distributed variables. The variables were stated as mean±standard deviation, the mean difference between groups, 95% confidence interval

(CI), frequency, and percentage. Student t-test for normally distributed variables and Chi-square test for nominal data were used. Level of significance was also set to p<0.05. Post hoc power analysis (G*Power 3.0.10 system, Franz Faul, Universität Kiel, Germany) was performed using ISWT data to compute achieved power regarding the difference between two independent means and percentages predicted of the distance of participants for an α value of 0.05, effect size of 0.50 and sample size group 1 (n=25) and 2 (n=22) which was presented as power (1-β) (22).

RESULTS

Demographic characteristics were similar in the myeloid and the lymphoid groups (p>0.05, Table 1). The score of ECOG performance status was one ("restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work") in all recipients of both groups. Transplantation characteristics were also summarized in Table 1. The stem cell sources for all recipients in the two groups were peripheral blood. Clinical characteristics were similar in the groups (p>0.05, Table 1), except both levels of albumin, which was lower in the lymphoid group compared to the myeloid group and rates of acute GvHD which was higher in the lymphoid group compared to the myeloid group (p<0.05). Rates of corticosteroid use before (myeloid: 5 (20%), lymphoid: 8 (36.4%)) and after (myeloid: 9 (36%), lymphoid: 11 (50%) HSCT were similar between the groups (p>0.05, Table 1).

Exercise Capacity

Only the percentage of ISWT distance (effect size d=0.97, power (1-β=0.89), but not ISWT distance (mean difference=66.73 m, over MCID, 95% CI=-57.72 to 191.18 m, effect size d=0.32, power (1-ß)=0.19), was significantly lower in the lymphoid group compared to the myeloid group (p<0.05, Table 2). The mean of ISWT distance was less than 80% of the predicted value in both groups (p>0.05, Table 2).

Pulmonary Function Test

No significant difference was observed in FEV_1, FVC, and PEF values between the groups (p>0.05, Table 2). The FEV_1/FVC and $FEF_{25-75\%}$ were significantly lower in the myeloid group compared to the lymphoid

Table 1: Demographic and Baseline Clinical Characteristics of Myeloid and Lymphoid Groups.

Characteristics	Myeloid Group (n=25)	Lymphoid Group (n=22)	p
	Mean±SD	Mean±SD	
Age (years)	42.76±14.72	37.27±14.13	0.200
Female (n, %)	9 (36)	7 (31.8)	1.000
Weight (kg)	68.82±8.54	64.48±10.51	0.126
Height (m)	1.65±0.07	1.67±0.07	0.288
Body Mass Index (kg/m²)	25.40±3.69	23.16±4.07	0.053
Smoking History (pack×years)	21.49±22.96	7.42±14.58	0.081
Blood Levels			
Hemoglobin (g/dL)	14.03±6.63	12.36±2.06	0.265
Platelet (mm³)	212192±73438.75	183327.27±82647.62	0.211
White Blood Cell (mm³)	6902.48±3134.30	5741.5±2497.34	0.171
Blood Glucose Level (mg/dL)	96.08±17.12	95.76±23.46	0.957
Albumin (g/dL)	4.29±0.30	4.05±0.37	**0.031***δ
Total Protein (g/dL)	6.74±0.67	6.61±0.65	0.563
Karnofsky Performance Status (0-100%)	94.40±6.51	95.91±5.90	0.412
Donor Types (n, %)			
HLA-Identical Sibling	17 (68)	17 (77.3)	
HLA-Matched Other Relative	3 (12)	0 (0)	0.420
HLA-Matched Unrelated	2 (8)	2 (9.1)	
HLA-Mismatched Unrelated	3 (12)	3 (13.6)	
Acute GvHD (n, %)	4 (16)	11 (50)	**0.026***#
Chronic GvHD (n, %)	7 (28)	10 (45.5)	0.214

*p<0.05. δStudent's t-test. #Chi-square test. HLA: Human Leukocyte Antigen, GvHD: Graft-versus-Host Disease.

Table 2: Comparison of Exercise Capacity, Pulmonary Function, Muscle Strength, and Quality of Life in Myeloid and Lymphoid Groups.

Characteristics	Myeloid Group (n=25)	Lymphoid Group (n=22)	Mean Difference (95% CI)	p
ISWT				
Distance (m)	704±211.60	637.27±211.10	66.73 (-57.72-191.18)	0.286
%Distance	73.26±13.34	60.47±13.11	12.79 (5.00-20.59)	**0.002***$^{\delta}$
Lung Function				
FEV_1 (%)	92.56±14.27	99.59±19.73	-7.03 (-17.06-2.99)	0.165
FVC (%)	97.72±9.83	98.77±20.48	-1.05 (-10.84-8.73)	0.827
FEV_1/FVC	78.72±8.38	85.71±4.97	-6.99 (-11.11--2.87)	**0.001***$^{\delta}$
PEF (%)	96.84±16.99	99.05±19.68	-2.21 (-12.98-8.57)	0.682
$FEF_{25-75\%}$ (%)	73.64±23.25	92.27±20.10	-18.63 (-31.49--5.78)	**0.005***$^{\delta}$
Quadriceps Femoris Strength				
Left (N)	258.68±72.19	256.05±72.14	2.64 (-39.86-45.13)	0.901
Left (%)	58.44±14.61	55.37±15.18	3.07 (-5.69-11.83)	0.484
Right (N)	262.52±56.06	262.05±67.78	0.48 (-35.92-36.87)	0.979
Right (%)	59.39±12.01	56.58±13.15	2.82 (-4.57-10.21)	0.447
Respiratory Muscle Strength				
MIP (cmH_2O)	121.88±24.4	106.64±23.99	15.24 (0.99-29.49)	**0.037***$^{\delta}$
MIP (%)	105.83±30.2	93.06±29.28	12.77 (-4.76-30.3)	0.149
MEP (cmH_2O)	146.72±33.06	122.55±38.29	24.18 (3.22-45.13)	**0.025***$^{\delta}$
MEP (%)	123.44±32.23	96.07±26.48	27.37 (9.89-44.85)	**0.003***$^{\delta}$
EORTCQLQ Subscales (0-100%)				
Global Health Status	72.67±18.09	65.91±25.71	6.76 (-6.17-19.69)	0.298
Functional	76.62±18.86	77.48±20.01	-0.85 (-12.28-10.57)	0.881
Social Functioning	69.33±28.33	69.69±30.7	-0.36 (-17.71-16.98)	0.967
Symptom	20.62±16.33	18.42±17.35	2.20 (-7.69-12.09)	0.656
Fatigue	34.22±24.19	30.3±24.05	3.92 (-10.28-18.13)	0.581

*p<0.05. $^{\delta}$Student's t-test. CI: Confidence interval. FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak expiratory flow, $FEF_{25-75\%}$: Forced expiratory flow from 25% to 75%, MIP: Maximal inspiratory pressure, MEP: Maximal expiratory pressure, ISWT: Incremental shuttle walk test, EORTCQLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

group (p<0.05, Table 2). Two (8%) recipients in the myeloid group and four (18.2%) recipients in the lymphoid group had restrictive airway disease, only three (12%) recipients in the myeloid group had obstructive airway disease (p>0.05). Small airway obstruction was also present in 16 (64%) recipients of the myeloid group and six (27.3%) recipients of the lymphoid group (p<0.05).

Respiratory Muscle Strength

No significant difference was observed in MIP% between the groups (p>0.05, Table 2). The MIP (mean difference=15.24 cmH_2O, over MCID), MEP, and MEP% values were significantly lower in the lymphoid group compared to the myeloid group (p<0.05, Table 2). While inspiratory muscle weakness existed in two (8%) recipients in the myeloid group and three (13.6%) recipients in the lymphoid group (p>0.05), expiratory muscle weakness existed in 13 (52%) recipients in the myeloid group and 20 (90.9%) recipients in the lymphoid group (p<0.05).

Quadriceps Strength

Right, and left quadriceps femoris muscle strength and its percentages of the predicted values were similar between the groups (p>0.05, Table 2). However, all means of both sides of quadriceps femoris muscle strength were less than 80% of the predicted value in both groups (p>0.05, Table 2).

Quality of Life

No significant difference was observed in global health status, functional subscale, social function subscale, symptom subscale, and fatigue subscale of EORTC QLQ-C30 between the groups (p>0.05, Table 2). There was a little change (6.76%, between 5% and 10%) in only global health status. Therefore, recipients of the lymphoid group had clinically lower quality of life level compared to others.

DISCUSSION

The retrospective analyses of the myeloid and lymphoid recipients firstly demonstrated that all allogeneic HSCT recipients have common clinically debilitating problems on exercise capacity (mean= 73.26% versus 60.47%, effect size d=0.97, power (1-ß)=0.89), lower extremity muscle strength (mean=58.44% versus 55.37%) and quality of life. Respiratory muscle weakness (especially in expiratory muscles, 90.9%) and apparently reduced maximal exercise capacity (66.73 m, over the MCID) are more prevalent in recipients with defects in lymphoid stem cells rather than recipients with defects in myeloid stem cells. Small airway obstruction was commonly observed in recipients with myeloid malignancies (64% versus 27.3%).

In accordance with the results of the present study, many studies in the literature have showed that both myeloid and lymphoid hematologic malignancies receiving high-dose chemotherapy generally experience decreased physical performance and impaired physiological condition (23) including respiratory and peripheral muscle weakness, decreased exercise capacity (24), sarcopenia (25), sarcopenia related to decreased muscle strength (25), evident sedentary lifestyle, and more reduced quality of life before HSCT (26). In addition, these impairments considerably deteriorate in the post-HSCT period compared to the pre-HSCT period (5,26,27). According to other outcomes of this study, the serum albumin level was lower, but in normal ranges, and also the presence of acute GvHD but not rates of corticosteroid usages was higher in lymphoid malignancies compared to myeloid malignancies. In parallel to the results of our recipients, protein and energy intakes decrease after HSCT despite taking protein supplements (28), and abnormalities in lower extremity muscle strength, exercise capacity, pulmonary functions (4) as well as muscle oxygenation (29) exist in especially allogeneic HSCT recipients. The present study demonstrated different types of impairments in recipients with two distinct types of hematologic malignancies. Based on the results of the study, it seems that recipients with lymphoid malignancies, including acute lymphoblastic leukemia, non-Hodgkin lymphoma, and multiple myeloma further suffer from impaired respiratory muscle strength and exercise capacity.

Meanwhile, recipients with myeloid malignancies, including acute myeloid leukemia, Myelodysplastic syndrome, and chronic myeloid leukemia suffer more from pulmonary involvements, especially in small airways which has also been supported by Kwok et al. (30). Especially after allogeneic HSCT, recipients may suffer from bronchiolitis obliterans syndrome, a severe and nadir respiratory complication of HSCT which is characterized by pulmonary function abnormalities and irreversible small airway narrowing due to the deposition of the scar tissue (31). Kwok et al. (30) suggested that acute myeloid leukemia (n=34, 35.8%), chronic myeloid leukemia (n=32, 33.7%) and myelodysplastic syndrome (n=8, 8.4%) were the most common underlying diagnosis in a total of 95 recipients with bronchiolitis obliterans syndrome. All of these diagnoses consist of myeloid malignancies, which may, therefore, demonstrate the recipients with myeloid malignancies might be candidates for bronchiolitis obliterans syndrome. Our results regarding these striking differences suggest that rehabilitation programs should better be modified according to the subtype of hematologic malignancy to ensure a better prognosis without complications.

Generally, specialists know that physical impairments may occur in hematologic malignancies both before and after HSCT process. Nevertheless, in clinical practice, specialists have not reached any practical information, which could indicate directly physical needs of a patient with hematologic malignancy according to the cell of origin. Since the power of our study based on percentage predicted value of the ISWT distance was sufficiently large (89%) enough to comment the results correctly, the results of the present study may provide compelling evidence regarding risk-adapted modification of rehabilitation programs. Because the current study demonstrated that although all recipients clinically have considerable decreased maximal exercise capacity, lower extremity muscle weakness, and more reduced quality of life, type of impairments might vary in lymphoid and myeloid disorders. According to our results, recipients with lymphoid malignancies experience expiratory muscle weakness, decreased maximal exercise capacity and lower albumin

levels, recipients with myeloid malignancies experience more abnormalities in small airways post-HSCT. Except for more frequent acute GvHD rates after HSCT in our recipients with lymphoid malignancies, these differences may result from abnormal DNA methylation of RUNDC3B (32). Methylation of RUNDC3B in acute lymphoblastic leukemia and its relation with a reduction in gene expression have been stated previously (33). It has not been observed in acute myeloid leukemia (34). Therefore, RUNDC3B, expressed in various tissues such as brain, thymus, ovary, testis, leukocytes, liver, small intestines and prostate (35), is a biomarker for diagnosis and prognosis in lymphoid malignancies including acute lymphoblastic leukemia and lymphomas (32). The RUNDC3B may have a vital role in the pathogenesis of lymphoid malignancies even after allogeneic HSCT survival. For this reason, further studies should investigate physical impairments of hematologic malignancies separately according to diagnosis origin, lymphoid or myeloid origin both before and after HSCT. Moreover, lymphoid and myeloid recipients received rehabilitation during HSCT process should be studied in terms of the relation between gene expression and these outcomes.

In conclusion, we presented a distinctive and discriminating perspective to evaluate and follow-up the physical condition and performance in allogeneic HSCT survivors related to cell of origin. In these recipients' group, exercise capacity, peripheral muscle strength, and quality of life should be assessed for all hematologic malignancies. Furthermore, respiratory muscle strength and exercise capacity in lymphoid malignancies, as well as pulmonary function in myeloid malignancies, should be reviewed separately. As to whether the malignancy is lymphoid or myeloid, the contents of rehabilitation programs should be adjusted individually in allogeneic HSCT recipients. Pulmonary rehabilitation, including aerobic exercise and respiratory muscle training, are crucial for all allogeneic recipients but especially for survivors with lymphoid cell disorder.

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Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Ethical Approval: The study protocol was approved by Gazi University Ethics Committee (Approval Date: 13.02.2018 and Approval Number: 2018-18).

Peer-Review: Externally peer-reviewed.

Author Contributions: Concept – GB, MBG, GTS; Design – GB, MBG; Supervision - GB, MBG, GTS; Resources and Financial Support – GB, MBG; Materials - GB, MBG; Data Collection and/or Processing – GB, MBG; Analysis and/or Interpretation – GB, MBG; Literature Research - GB, MBG; Writing Manuscript – GB, MBG; Critical Review – GB, MBG, GTS.

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