ISSN: 2651-4451 • e-ISSN: 2651-446X

Türk Fizyoterapi ve Rehabilitasyon Dergisi

2019 30(2)81-88

Vesile YILDIZ KABAK, MSc, PT[1]
Hakan GÖKER, MD[2]
Songül ATASAVUN UYSAL, PhD, PT[1]
Haluk DEMİROĞLU, MD[2]
Elifcan ALADAĞ KARAKULAK, MD[2]
Müfide OKAY, MD[2]
Tülin DÜGER, PhD, PT[1]

1 *Hacettepe University, Faculty of Physical Therapy and Rehabilitation, Ankara, Turkey.*
2 *Hacettepe University, Faculty of Medicine, Department of Hematology, Ankara, Turkey.*

İletişim (Correspondence):

Tülin DÜGER, PhD, PT
Hacettepe University,
Faculty of Physical Therapy and Rehabilitation,
06100 Samanpazari, Ankara, Turkey
Phone: +90-312-305 1576
E-mail: tduger@yahoo.com
ORCID: 0000-0002-3332-5958

Vesile YILDIZ KABAK
E-mail: vesile_yldz@hotmail.com
ORCID: 0000-0002-1559-1793

Hakan GÖKER
E-mail: hgoker1@yahoo.com
ORCID: 0000-0002-1039-7756

Songul ATASAVUN UYSAL
E-mail: songula@hacettepe.edu.tr
ORCID: 0000-0001-7344-411X

Haluk DEMİROĞLU
E-mail: halukd@hacettepe.edu.tr
ORCID: 0000-0002-6790-8748

Elifcan ALADAĞ KARAKULAK
E-mail: elifcan.aladag@hacettepe.edu.tr
ORCID: 0000-0002-1206-9908

Müfide OKAY
E-mail: mufide.okay@hacettepe.edu.tr
ORCID: 0000-0001-5317-0597

Geliş Tarihi: *26.12.2018 (Received)*
Kabul Tarihi: *02.05.2019 (Accepted)*

DETERMINANTS OF CARDIORESPIRATORY FITNESS LEVEL IN HEMATOPOIETIC STEM CELL TRANSPLANTATION CANDIDATES

ORIGINAL ARTICLE

ABSTRACT

Purpose: This study aimed to investigate cardiorespiratory fitness level and to determine predictors of cardiorespiratory fitness level in hematopoietic stem cell transplantation (HSCT) candidates.

Methods: Seventy-six patients between the age of 18 and 65 years (45 males, and 31 females) who firstly hospitalized for HSCT at Hacettepe University HSCT Service were included. The 6-minute walk test (6MWT) was used to assess cardiorespiratory fitness level. Hand grip and peripheral muscle strength were assessed using a hand-held dynamometer. The 30-S chair-stand test was used to assess lower limb muscle endurance. Functional mobility was assessed using the Time up and go test-3 meters (TUG-3m). The Fatigue Severity Scale, Hospital Anxiety and Depression Scale, and European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire were used to assess fatigue, emotional status, and quality of life, respectively.

Results: Participants had lower 6MWT distance than predicted reference values (mean difference: 69.27 m, $p<0.001$) and females had lower cardiorespiratory fitness level than males ($p=0.032$). Age, peripheral muscle strength, and TUG-3m had moderate to high correlation with the 6MWT distance ($p<0.001$). Age, knee muscle strength, and TUG-3m were determined as independent predictors, explaining 78% of variance in 6MWT distance ($r=0.887$, $r^2=0.736$, $F_{(2,38)}=45.33$, $p<0.001$).

Conclusion: Candidates for HSCT has impairment in cardiorespiratory fitness and this associated with individual and clinical factors. Not only aerobic exercise but also exercises aiming to increase, especially, knee extensor muscle strength and functional mobility should be performed to increase cardiorespiratory fitness in patients undergoing HSCT.

Key Words: Cardiorespiratory Fitness; Hematopoietic Stem Cell Transplantation; Muscle Strength.

HEMATOPOİETİK KÖK HÜCRE TRANSPLANTASYONU ADAYLARINDA KARDİYOPULMONER UYGUNLUK DÜZEYİNİN BELİRLEYİCİLERİ

ARAŞTIRMA MAKALESİ

ÖZ

Amaç: Çalışmamızın amacı, hematopoietik kök hücre transplantasyonu (HKHT) adaylarında kardiyopulmoner uygunluk düzeyinin araştırılması ve kardiyopulmoner uygunluk düzeyi ile ilişkili faktörlerin belirlenmesiydi.

Yöntem: 18-65 yaşları arasında, ilk kez HKHT için Hacettepe Üniversitesi Kemik İliği Transplantasyonu Servisi'ne yatırılan 76 birey (45 erkek ve 31 kadın) dahil edildi. Altı dakika yürüme testi (6DYT), kardiyopulmoner uygunluk düzeyini belirlemede kullanıldı. Kavrama ve periferal kasların kuvveti elde tutulan dinamometre ile ölçüldü. Alt ekstremite kas enduransı 30 sn otur kalk testi ile değerlendirildi. Fonksiyonel mobilite zamanlı kalk yürü testi-3 metre (TUG-3 m) ile ölçüldü. Yorgunluk Şiddet Ölçeği yorgunluk, emosyonel durum Hastane Anksiyete ve Depresyon Ölçeği ve yaşam kalitesini Avrupa Kanser Araştırmaları ve Tedavi Organizasyonu–Yaşam Kalitesi Anketi ile değerlendirildi.

Sonuçlar: Katılımcılar tahmin edilen referans değerler ile karşılaştırıldığında istatistiksel olarak daha düşük 6DYT mesafesine sahipti (ortalama fark: 69,27 m, $p<0,001$) ve kadınlar erkeklere göre daha düşük kardiyopulmoner uygunluk düzeyine sahipti ($p=0,032$). Yaş, periferal kas kuvveti ve TUG-3 m orta-yüksek derecede 6DYT mesafesi ile ilişkiliydi ($p<0,001$). Yaş, diz ekstansiyon kas kuvveti ve TUG-3m skorları 6DYT mesafesindeki değişimin % 78'ini açıklayan bağımsız belirteçler olarak belirlendi ($r=0,887$, $r^2=0,736$, $F_{(2,38)}=45,33$, $p<0,001$).

Tartışma: HKHT için hastaneye yatırılan bireylerde kardiyopulmoner uygunluk düzeyi azalır ve bu kişisel ve klinik faktörler ile ilişkilidir. Aerobik egzersizlerin yanı sıra özellikle diz ekstansiyonu kas kuvvetini ve fonksiyonel mobiliteyi artırmaya yönelik egzersizler, HKHT uygulanan bireylerin kardiyopulmoner uygunluk düzeyini artırmada kullanılmalıdır.

Anahtar Kelimeler: Kardiyopulmoner Uygunluk; Hematopoietik Kök Hücre Transplantasyonu; Kas Kuvveti.

INTRODUCTION

Along with the improvement in treatment options and constant evolution in its technology, hematopoietic stem cell transplantation (HSCT) has been using for more patients who had malign or non-malignant hematological diseases. In addition, the development of less aggressive treatments has expanded the use of HSCT to older patients and those with comorbidities (1). According to a report gathered by 1566 teams from 77 countries in 2016, HSCT was performed for over than 60000 individuals in the world and when compared with the 2006 an increase of 46% was reported (2). As a result of these improvements, the side effects of this aggressive treatment have become a more crucial issue for researches studying in this field (3).

Cardiorespiratory fitness (CRF) is a significant predictor of health and survival rate in individuals diagnosed with cancer (4,5). It is also a significant predictor for clinical outcomes and length of hospital staying in cancer patients (6,7). Along with these results, determination of CRF level at the initial phase of the HSCT may give information to health professionals about tolerance to the treatments during HSCT process. Moreover, detecting the CRF level as early as possible can contribute to developing interventions aiming to decrease impairment in CRF.

There is limited information regarding the CRF level and the associated factors in HSCT candidates. In one study, CRF level was lower in HSCT candidates than healthy controls, and it was associated with age, hemoglobin level, and treatment variables. In the study, there was no relationship between knee extension strength, quality of life, and CRF (8). In the present study, we hypothesized that patients had impairment in CRF before HSCT, which was associated with demographic, medical and clinical characteristics. Therefore, we aimed to determine the CRF level in candidates for HSCT by comparing normal data and further investigate the determinants of CRF in these subjects.

METHODS

This study was a descriptive study and conducted at Hacettepe University Oncology Hospital Bone Marrow Transplantation Service in Ankara, Turkey. Patients aged between 18 and 65 years, who planned to HSCT, were included in the present study. The same physiotherapist assessed participants within the first seven days of hospitalization. The assessments were postponed or canceled, if the presence of severe neutropenia, severe infection, thrombocytopenia or anemia. Patients who hospitalized for HSCT treatment firstly, being able to walk without any device, without a severe cardiopulmonary or neurologic problem, willing to participate were included in the present study. The sample size was determined as at least 46 participants, according to the power analysis with the 80% power and the 95% confidence interval for moderate or higher Pearson correlation coefficient (rho≥0.40). Written informed consent was obtained from all included patients. This study was approved by the Ethics Committee of Hacettepe University (GO 16/286).

Outcome Variables

Patients' demographic data (age, educational status, body mass index) and current smoking status were recorded. The medical variables (diagnosis, duration after diagnosis, comorbidities, and previous treatment history) of the individuals were recorded from hospital records. In addition, patients were verbally asked for whether they do regular exercise or do not since they diagnosed with cancer and their response was recorded as "Yes" or "No."

Cardiorespiratory Fitness

The 6-minute walk test (6MWT) was used to evaluate the CRF level, and the test was performed according to the European Respiratory Society/ American Thoracic Society technical standards for field tests (9,10). Briefly, patients were instructed to walk a 30-m corridor as fast as possible, without jogging or running. Patients were permitted to rest if needed, or the test was stopped in case of severe dyspnea or dizziness, and the test was repeated for one time to avoid fatigue. The total distance covered at the end of six minutes was recorded. This test was found valid, reliable, and indicator of functional capacity in individuals diagnosed with cancer (11). The age- and sex-predicted 6MWT distance was calculated from the equation provided by Enright and Sherrill. (12).

Hand Grip Strength

To assess grip strength, a standard adjustable-handle dynamometer (Jamar Hydraulic Hand Dynamometer (JA Preston Corporation, Clifton, NJ, USA) was used. This test was performed following the guidelines of the American Society of Hand Therapists (13). The mean score of three trials for the dominant side was recorded as kilograms-force. Handgrip strength has been validated as an indicator of upper extremity strength (14).

Peripheral Muscle Strength

Digital hand-held dynamometer (J Tech Medical, J Tech Commander PowerTrack II, Salt Lake City, UT, USA) was used to measure peripheral muscle strength of the participants. Evaluation of the dominant side muscle strength was performed for shoulder flexors, elbow flexors, knee extensors, and hip flexor muscles. Measurements were repeated for three times, and the mean score was recorded as Newton (15). The test and patient positions were performed according to the statements of Bohannon (16) and the manufacturer's manual. The same physiotherapist performed all the tests.

Functional Mobility

The timed up and go-3 m (TUG-3m) test was used to evaluate functional mobility. This test measures the time needed to stand up from a seated position in a chair, walk 3 m, turn around, return to the chair, and sit down. Elapsed time was measured with a stopwatch and recorded in seconds (17).

Lower Limb Muscle Endurance

The 30-s chair-stand test was used to assess lower limb muscle endurance. The 30-s chair-stand test involves recording the number of stands (sitting in a chair to standing erect) that a subject can complete in 30-s. The test has been validated as an indicator of lower body muscle endurance. The total number of stands that were correctly and fully executed within the 30-s time frame was recorded (18).

Fatigue

The Fatigue Severity Scale was used to assess the severity of fatigue in participants. This scale has nine items, each of which is scored 1 (strongly disagree) to 7 (strongly agree). Higher scores represent greater fatigue severity. The cut-off point for pathological fatigue is determined as ≥4 points. The Turkish version of the Fatigue Severity Scale was used and the required permission was obtained (19,20).

Emotional Status

The Hospital Anxiety and Depression Scale was used to measure the emotional status of participants using parameters including anxiety and depression. This scale has seven items for anxiety and seven items for depression. Responses are scored on a scale of 0 to 3, and higher scores indicate higher anxiety/depression level. The Turkish version of this form was used and the required permission from the corresponding author was taken (21,22).

Quality of Life

Health-related quality of life was assessed using the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire. This scale has three different domains including general health, functional score, and symptom score. The patient is requested to rank each of the items on a scale ranging from 1 (not at all) to 4 (very much). Higher scores indicate higher general health and functioning; and also lower symptom severity. Turkish version of this scale was used in the present study, and the required permission was provided (23).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 15.0 software (SPSS Inc., Chicago, IL, USA). The level of significance was set at 0.05 for all statistical analyses, and results are expressed as a percentage or mean±standard deviation. The Kolmogorov–Smirnov test was used to determine the normality of distribution. Student t test or Mann Whitney U test was used to compare mean values of 6MWT between subjects and norm values, and to compare 6MWT results according to gender, presence of comorbidity, and previous exercise habit. The 95% confidence interval was computed for the mean difference between two groups. To assess correlations between assessed parameters, Spearman correlation coefficient test was used. Multiple

linear regression analysis was performed to determine the factors predicting 6MWT. The model fit was assessed using appropriate residual and goodness-of-fit statistics.

RESULTS

Totally 76 patients, 45 males (59.2%) and 31 females (40.8%) who mostly had a malignant hematological disease and were decided to receive HSCT treatment included in the present study. All of the patients received chemotherapy treatment between diagnosis and HSCT. Demographic and medical characteristics of the participants are showed in Table 1. Our subjects mostly diagnosed with lymphoma and according to the mean body mass index, they were overweight. All of the participants currently do not smoking. In addition, 65% of participants had no regular exercise habits. Thirty-seven percent of the patients had some comorbidities, yet all of those can complete 6MWT and other tests without an adverse event. In addition, none of the participants currently were smoking.

The scores of outcome parameters including the 6MWT, hand grip, and peripheral muscle strength measurements, the 30-S chair-stand test, the TUG-3m test, the Fatigue Severity Scale, the Hospital Anxiety and Depression Scale, and the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire scores are showed in Table 2. When 6MWT results were compared between participants and age, sex, height, and weight-matched norms, they had lower cardiopulmonary fitness than norm data, which was around 86% of expected value (437.63±73.65 vs. 506.9±66.57 m; mean difference=69.27 m, 95% Confidence Interval=35.16-103.37 m, $p<0.001$). In addition, female patients walked significantly less than male patients (412.69±78.94 vs. 460.79±62.41 m, mean difference=48.1 m, 95% Confidence Interval=8.08-104.29, $p=0.032$).

When participants were compared according to the presence of comorbidity, there was no significant difference between groups ($p>0.05$). On the other

Table 1: Demographic and Medical Characteristic of Hematopoietic Stem Cell Transplantation Candidates.

Parameters	HSCT Candidates (n=76)	Min-Max
Age (years)	44.89±15.49	18-65
Body Mass Index (kg/m²)	26.69±5.75	16.97-40.90
Diagnosis, n (%)		
Lymphoma	35	46
Multiple Myeloma	22	28.9
Leukemia	10	13.1
Other	9	11.8
Duration after Diagnosis (months)	15.19±13.6	3-60
Chemotherapy Cycles (n)	5.01±0.97	4-6
Comorbidity, n (%)		
Diabetes Mellitus	4	5.4
Hypertension	4	5.4
Cardiac Disease	4	5.4
Lung Disease	3	4.1
Seconder Cancer	3	4.1
Coronary Artery Disease	3	4.1
Chronic Kidney Disease	2	2.7
Other	4	5.4
None	49	63
Educational Status, n (%)		
Illiterate	7	9.2
Elementary School	28	36.8
Secondary School	9	11.8
High School	11	14.4
University	21	27.6
Previous Exercise Habit, n (%)		
Yes	26	34.2
No	50	65.7

HSCT: Hematopoietic Stem Cell Transplantation.

Table 2: Cardiopulmonary Fitness, Muscle Strength, Functional Mobility, Fatigue, Emotional Status, and Quality of Life Level of the Participants.

Parameters	HSCT Candidates (n=76) Mean±SD	Min-Max
6MWT (m)	437.63±73.65	300-615
Grip Strength (kgf)	23.31±10.23	4.30-49.64
Muscle Strength (N)		
Hip Flexors	96.53±27.59	46.90-169
Knee Extensors	99.33±28.80	61.60-170
Shoulder Flexors	86.73±25.74	30.07-169
Elbow Flexors	89.47±24.18	41.80-151.67
TUG-3m (s)	9.53±3.17	5-16
30-s Chair-Stand Test (n)	14.26±3.78	3-25
FSS Score	37.77±15.41	9-63
HADS Score		
Anxiety	6.34±4.69	0-21
Depression	6.63±4.87	0-21
EORTC QLQ-C30 Score		
General Health	52.01±25.32	0-100
Functional	66.26±19.03	30.76-100
Symptom	31.63±17.84	0-74.35

HSCT: Hematopoietic Stem Cell Transplantation, 6MWT: 6 Minute Walk Test, TUG-3m: Time Up and Go-3 meters, FSS: Fatigue Severity Scale, HADS: Hospital Anxiety and Depression Scale, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire.

hand, participants who had regular exercise habit walked significantly further according to 6MWT than who had not such a habit (516.77±73.9 vs. 454.88±80.89 m, mean difference=61.89 m, p=0.037).

The associated factors were analyzed, and there were positive and moderate correlations between grip strength, peripheral muscle strength, and 6MWT distance (p<0.05). In addition, negative and strong correlations were found between age, the TUG-3m, and 6MWT distance (p=0.001). The correlation analyzes are showed in Table 3. There was no correlation between other outcome parameters and CRF level in the subjects.

A multiple linear regression analysis was performed using those factors found to be significant by univariate analysis including age, gender, grip strength, peripheral muscle strength, and TUG-3 m test. Multiple linear regression analysis yielded that age, knee extension muscle strength, and TUG-3m scores were the independent predictors of 6MWT distance, explaining 78% of the variance. The equation was as follows: 6MWT distance (m) = 669.9+(Knee extension muscle strength×0.86)–(Age×1.53)–(TUG-3m×25.22); r=0.887, r^2=0.736, $F_{(2,38)}$=45.33, p<0.001.

DISCUSSION

In this study, CRF level of HSCT candidates was significantly lower than norm data (around 70 m, 86% of predicted value). The 6MWT distance was correlated with age, peripheral muscle strength, and functional mobility of the participants. On the other hand, 6MWT distance was higher in male patients having regular exercise habit. Moreover, age, knee extension muscle strength, and TUG-3m scores were the independent predictors of 6MWT

Table 3: Factors Correlated with Six-Minute Walk Test before Hematopoietic Stem Cell Transplantation.

Outcomes	Age		Grip Strength		Peripheral Muscle Strength						TUG-3m	
					Hip Flexors		Knee Extensors		Elbow Flexors			
	r	p	r	p	r	p	r	p	r	p	r	p
6MWT	-0.635	**0.001***	0.436	**0.003***	0.346	**0.017***	0.469	**0.001***	0.404	**0.006***	-0.777	**0.001***

*p<0.05. Spearman Correlation Coefficient Test, only significant correlation coefficients were presented. 6MWT: 6-Minute Walk Test, TUG-3m: Time Up and Go-3 meters.

in candidates for HSCT.

Cardiopulmonary fitness is an essential component of health and one of the predictors of mortality risk in cancer patients (5). In a study pre-transplant, 6MWT distance was found as significant predictor of clinical outcomes in patients following allogeneic HSCT (24). In the present study, we aimed to find out all aspects of physical function, symptoms, and patient-reported outcomes in individuals preparing for HSCT, and to explore associations between CRF levels in this population.

Sixty-five percent of the individuals had no exercise habit, which was considerably high, yet this rate was consistent with other studies conducted on healthy Turkish population (25). In agreement with the result, a low level of physical activity was also reported in a study on candidates of HSCT (26). The 6MWT distance, grip strength, quality of life, and anxiety and depression scores in our population were slightly lower but similar to the other studies conducted on HSCT patients (8). In addition, according to the Fatigue Severity Scale, a high level of fatigue was noted.

Following other studies conducted on patients undergoing HSCT, patients had significantly lower (around 70m in 6MWT distance) CRF level when compared with the norm value in the pre-sent study. Since the measured distance was 86% of the predicted value, and this can be accepted as in a normal range. However, when considering patients undergoing aggressive therapies through HSCT process, CRF level should be protected and maintained at high level by doing exercise. Moreover, the females had lower fitness level than male patients, which was similar to a study investigating gender differences in patients in the early phase following allogeneic HSCT (26). However, according to the regression analysis gender was not a determinant for CRF in patients before HSCT in the present study. Only age was found as a demographic predictor for 6MWT distance. We suggested that patients who were older should be carefully followed and referred to appropriate exercise program to increase aerobic capacity before the HSCT protocols.

In a study conducted on lymphoma survivors who treated with HSCT, the results were similar with our study that peak oxygen consumption was lower than normal value in which 4.5% lower in females and 7.7% in males. In addition, current smoking status, impaired diffusion capacity, and physical activity level were associated with CRF level (27). In another study, moderate-to-vigorous physical activity was correlated with the 6MWT distance in patients undergoing allogeneic HSCT (28). In our study, current physical activity level could not be measured because of the limited time before HSCT. In future studies, physical activity may be further investigated in individuals undergoing HSCT.

The leg extension torque was indicated a predictor related to peak oxygen consumption before HSCT in a study investigating factors related to CRF (29). Further relationships were found in the present study between CRF and other physical function parameters assessed. Not only leg extension muscle strength, but also hip flexor muscle strength and upper body muscle strength were correlated with 6MWT distance in the present study. Regression analysis revealed that knee extension muscle strength was an independent determinant of 6MWT. There is some evidence that because lower extremity muscle strength directly affects functional activities, especially quadriceps femoris muscle strength was related to cardiopulmonary fitness (30). To increase CRF level, not only aerobic exercises but also muscle strengthening exercises especially for quadriceps femoris muscle should be performed for patients preparing for HSCT and during HSCT treatment process. Besides muscle strength, functional mobility (TUG-3m) was also found a predictor of 6MWT distance. This association may have contributed to an increase in mobility which may positively affect participation in daily activities and sports, and this may lead to an increase in CRF level. Since there is no previous study using the TUG-3m test conducted on this population, for this reason, it was difficult to compare our results with the current literature.

We had some limitations in this study. First of all, a laboratory test could not be used for assessing CRF level. Because 6MWT is easy to conduct in the hospital setting, we selected this clinical measurement test. In addition, the physical activity level of the participants could not be detailed and objectively measured. Our strengths were besides univariate

analysis, multivariate regression analysis was performed to determine predictors of CRF. Moreover detailed physical measurements and patient-reported outcomes were also investigated to determine factors to predict CRF level.

In conclusion, HSCT candidates had impairment in CRF, and age, knee extension muscle strength, and functional mobility were the determinants of 6MWT. We suggested that these factors should be carefully considered in patients preparing to HSCT protocol. Moreover, patients under these risk factors should be a referral to exercise therapy as early as possible to maintain or to increase CRF level. We suggest that besides aerobic exercise, muscle strengthening exercises, especially for quadriceps femoris and exercises for functional mobility, positively affect CRF level of individuals before HSCT.

Sources of Support: None.

Conflict of Interest: The authors have no conflicts of interest.

Ethical Approval: The ethical approval of the Ethics Committee was obtained from Hacettepe University Non-Interventional Clinical Researches Ethics Committee (GO 16/286).

Informed Consent: Written informed consent was taken from all participants.

Acknowledgements: None.

REFERENCES

1. Schmit-Pokorny K. Expanding indications for stem cell transplantation. Semin Oncol Nurs. 2009;25(2):105-14.
2. Niederwieser D, Baldomero H, Szer J, Gratwohl M, Aljurf M, Atsuta Y, et al. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. Bone Marrow Transplant. 2016;51(6):778-85.
3. Gruber U, Fegg M, Buchmann M, Kolb HJ, Hiddemann W. The long term psychosocial effects of haematopoetic stem cell transplantation. Eur J Cancer Care. 2003;12(3):249-56.
4. Schmid D, Leitzmann M. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. Ann Oncol. 2014;26(2):272-8.
5. Jensen MT, Holtermann A, Bay H, Gyntelberg F. Cardiorespiratory fitness and death from cancer: a 42-year follow-up from the Copenhagen Male Study. Br J Sports Med. 2017;51(18):1364-9.
6. Chandrabalan VV, McMillan DC, Carter R, Kinsella J, McKay CJ, Carter CR, et al. Pre-operative cardiopulmonary exercise testing predicts adverse post-operative events and non-progression to adjuvant therapy after major pancreatic surgery. HPB (Oxford). 2013;15(11):899-907.
7. Jones LW, Watson D, Herndon JE, Eves ND, Haithcock BE, Loewen G, et al. Peak oxygen consumption and long term all cause mortality in nonsmall cell lung cancer. Cancer. 2010;116(20):4825-32.
8. Morishita S, Kaida K, Ikegame K, Yoshihara S, Taniguchi K, Okada M, et al. Impaired physiological function and health-related QOL in patients before hematopoietic stem-cell transplantation. Support Care Cancer. 2012;20(4):821-9.
9. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44 (6):1428-46.
10. Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1447-78.
11. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the six-minute walk test in cancer patients. Int J Sports Med. 2013;34(7):631-6.
12. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1384-7.
13. Balogun JA, Akomolafe CT, Amusa LO. Grip strength: effects of testing posture and elbow position. Arch Phys Med Rehabil. 1991;72(5):280-3.
14. Kallman DA, Plato CC, Tobin JD. The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. J Gerontol. 1990;45(3):82-8.
15. Adams GM. Exercise physiology laboratory manual: Dubuque (IA); 1990.
16. Bohannon RW, Andrews AW. Interrater reliability of hand-held dynamometry. Phys Ther. 1987;67(6):931-3.
17. Bohannon RW. Reference values for the timed up and go test: a descriptive meta-analysis. J Geriatr Phys Ther. 2006;29(2):64-8.
18. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 70(2):113-9.
19. Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, et al. The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. Int J Rehabil Res. 2007;30(1):81-5.
20. Krupp LB, Christodoulou C. Fatigue in multiple sclerosis. Curr Neurol Neurosci Rep. 2001;1(3):294-8.
21. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. J Psychosom Res. 2002;52(2):69-77.
22. Aydemir Ö, Guvenir T, Kuey L, Kultur S. Validity and reliability of Turkish version of hospital anxiety and depression scale. Turk Psikiyatri Derg. 1997;8(4):280-7.
23. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: J Natl Cancer Inst. 1993;85(5):365-76.
24. Jones LW, Devlin SM, Maloy MA, Wood WA, Tuohy S, Espiritu N, et al. Prognostic importance of pretransplant functional capacity after allogeneic hematopoietic cell transplantation. Oncologist. 2015;20(11):1290-7.
25. Aslan D, Özcebe H, Temel F, Takmaz S, Topatan S, Şahin A, et al. What influences physical activity among elders? A Turkish experience from Ankara, Turkey. Arch Gerontol Geriatr. 2008;46(1):79-88.
26. Morishita S, Kaida K, Yamauchi S, Wakasugi T, Yoshihara S, Taniguchi K, et al. Gender differences in health related quality of life, physical function and psychological status among patients in the early phase following allogeneic haematopoietic stem cell

transplantation. Psychooncology. 2013;22(5):1159-66.
27. Stenehjem JS, Smeland KB, Murbraech K, Holte H, Kvaløy S, Thorsen L, et al. Cardiorespiratory fitness in long-term lymphoma survivors after high-dose chemotherapy with autologous stem cell transplantation. Br J Cancer. 2016;115(2):178-87.
28. Morishita S, Kaida K, Yamauchi S, Wakasugi T, Ikegame K, Ogawa H, et al. Relationship of physical activity with physical function and health related quality of life in patients having undergone allogeneic haematopoietic stem cell transplantation. Eur J Cancer Care. 2017;26:e12669.
29. Ishikawa A, Otaka Y, Kamisako M, Suzuki T, Miyata C, Tsuji T, et al. Factors affecting lower limb muscle strength and cardiopulmonary fitness after allogeneic hematopoietic stem cell transplantation. Support Care Cancer. 2019;27(5):1793-1800.
30. Carvalho LP, Di Thommazo-Luporini L, Aubertin-Leheudre M, Junior JCB, De Oliveira CR, Luporini RL, et al. Prediction of cardiorespiratory fitness by the six-minute step test and its association with muscle strength and power in sedentary obese and lean young women: a cross-sectional study. PloS One. 2015;10(12):e0145960.