

Association between physical function and health-related quality of life in survivors of hematological malignancies undergoing hematopoietic stem cell transplantation

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Abstract

Objective: The association between physical function and the health-related quality of life (HRQOL) remains unclear in survivors of hematological malignancies undergoing hematopoietic stem cell transplantation (HSCT). The purpose of this study is to clarify the association between physical function and HRQOL in survivors of hematological malignancies undergoing HSCT.

Methods: The present cross-sectional multicenter study included 32 survivors of hematological malignancies who underwent HSCT. Patient characteristics, physical function (based on handgrip strength, isometric knee extension strength, 6-minute walk test [6MWT], and chair stand test), HRQOL (assessed with the 36-Item Short-Form Health Survey [SF-36] questionnaire), depression, fatigue, and physical activity level were assessed.

Results: A significant association was observed between physical function (chair stand test and 6MWT) and the physical functioning (PF) subscales of the SF-36 questionnaire. The PF, mental health, and social functioning (SF) subscales of the SF-36 questionnaire were significantly associated with depression and fatigue. Multiple logistic regression analysis showed that the physical component summary was significantly associated with depression and affective fatigue, and the PF score was significantly associated with the chair stand test and depression. The mental component summary showed that the physical role functioning, vitality, and SF scores were also significantly associated with depression.

Conclusion: Physical function, depression, and fatigue were significantly associated with the HRQOL in survivors of hematological malignancies undergoing HSCT.

Abbreviations: allo-HSCT: allogeneic hematopoietic stem cell transplantation; ATS: American Thoracic Society; BP: bodily pain; CFS: Cancer Fatigue Scale; GH: general health; GVHD: graft-versus-host disease; HRQOL: health-related quality of life; HSCT: hematopoietic stem cell transplantation; IPAQ: International Physical Activity Questionnaire; MCS: mental component summary; MET: metabolic equivalent of task; NBS: norm-based scores; NCCN: National Comprehensive Cancer Network; PA: physical activity level; PCS: physical component summary; PF: physical functioning; RE: emotional role functioning; RP: physical role functioning; SDS: Self-Rating Depression Scale; SF: social functioning; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; SPPB: short physical performance battery; VT: vitality; 6MWT: 6-minute walk test

Introduction

Hematopoietic stem cell transplantation (HSCT) well-established standard treatment for patients with a variety of hematological

malignancies and is associated with good clinical outcomes with longer post-transplant life expectancy being observed over the years [1]. Notably, improved overall survival is not the only determinant of successful medical outcomes following HSCT; therefore, health-related quality of life (HRQOL) is being considered as one of the useful indicators for successful treatment [2]. Previous studies have reported that age at transplantation, sex, marital status, primary diagnosis,

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infection, graft-versus-host disease (GVHD), and sibling donor, are among the factors associated with the HRQOL in patients undergoing HSCT [3-5].

Physical activity levels are markedly reduced in patients undergoing HSCT owing to the conditioning regimen, such as the administration of total body irradiation, high-dose chemotherapy, immunosuppressive therapy for GVHD, transplant-related toxicities including infections and GVHD, and prolonged bed rest in a bio-clean room. Therefore, deconditioning is commonly observed in patients undergoing HSCT [6-8]. Physical function (represented by muscle strength and aerobic capacity) is decreased after HSCT [8-10]. Deconditioning that occurs during treatment limits patients' leisure and occupational activities; therefore, resumption of daily activities after discharging from hospital becomes difficult and negatively affects patients' HRQOL [11]. Previous studies report a period of up to one year for complete recovery of physical function in 40% of patients undergoing allogeneic HSCT (allo-HSCT). Moreover, stamina loss prevented 32% of survivors from return to work during the first 2 years after allo-HSCT [12].

Therefore, physical function is an important factor associated with the HRQOL in patients who undergo HSCT, although to date, the association between physical function and HRQOL remains unclear. We investigated the association between physical function and HRQOL in survivors of hematological malignancies undergoing HSCT.

Methods

Participants

This cross-sectional multicenter study included 32 survivors of hematological malignancies who underwent HSCT and presented for outpatient medical follow-up after discharge at Kobe University Hospital and Kakogawa Central City Hospital in Japan between June and November 2014. This study was performed in accordance with the ethical standards established by the 1964 Declaration of Helsinki and later amendments and was approved by the Ethics Committee of Kobe University Graduate School of Health Sciences (approval number: 298-1). Written informed consent was obtained from all participants.

Measures

Patient characteristics

The following data were obtained from the medical records: age, sex, primary diagnosis, graft type (autologous/allogeneic), donor type (bone marrow/peripheral blood/umbilical cord blood), conditioning regimen (myeloablative/non-myeloablative), and interval between transplantation and study enrollment.

Physical Function

Handgrip strength, isometric knee extension strength, 6-minute walk test (6MWT), and chair standing test were evaluated as variables of physical function.

Handgrip strength was measured using a standard adjustable-handle dynamometer (Grip-D, Takei Scientific Instruments Co. Ltd., Niigata, Japan) in accordance with the method previously described by Mathiowetz, *et al.* [13]. The grip dynamometer was set to the second grip position. The test was performed twice on each hand and the highest value was selected for analysis.

Isometric knee extension strength was measured using a hand-held dynamometer (microFET2; Nihon Medix, Chiba, Japan) based on

the method described by Andrews, *et al.* [14]. The test was performed with the patient seated and the knee flexed to approximately 90°. The dynamometer was applied proximal to the malleoli. The maximum force observed during 10 s of effort was recorded. The test was performed twice on each leg, and the highest value was selected for analysis.

Exercise capacity was evaluated using 6MWT based on the American Thoracic Society (ATS) guidelines [15]. Patients were instructed to walk along a 10 m corridor for 6 min at their own pace. They were encouraged to cover as much distance as was possible; however, they were permitted to stop for rest and resume as soon as they felt able. The test was aborted in patients who experienced symptoms of dyspnea or leg pain. The distance covered in 6 min was recorded.

The chair stand test was performed based on the short physical performance battery (SPPB), and the time required for 5-repetition sit-to-stand was recorded [16].

Health-related quality of life (HRQOL)

The HRQOL was evaluated using the Japanese version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [17]. SF-36 is a self-administered questionnaire that evaluated general health-related QOL and assesses physical and mental health components across 8 domains: physical functioning (PF), physical role functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role functioning (RE), and mental health (MH). HRQOL is a multidimensional construct; SF-36 assesses the key components that constitute the HRQOL on a scale of 0-100, with higher scores indicating better HRQOL. The scores obtained after assessment of all 8 domains are combined to calculate more comprehensive indicators of physical and mental health: the physical component summary (PCS) and the mental component summary (MCS) scores. PCS and MCS are converted into norm-based scores (NBS) applicable to the general Japanese population [17]. A score of 50 points indicates the national standard value of the NBS, and higher scores indicate a better HRQOL.

Depression

Depression was assessed with the Self-Rating Depression Scale (SDS) [18]. SDS is a 20-item self-report questionnaire that is widely used as a screening tool covering affective, psychological, and somatic symptoms associated with depression. Each item is scored on a Likert scale with scores ranging from 1-4. The total score is obtained by calculating the sum of individual item scores and ranges from 20-80. Most patients with depression score between 50 and 69 points, and scores of >70 indicate severe depression.

Fatigue

The Cancer Fatigue Scale (CFS) was used to assess fatigue [19]. CFS is a 15-item self-rating scale to assess fatigue of cancer patients. The scale consists of 3 subscales (scales evaluating the physical, affective, and cognitive aspects of fatigue) and assesses the multidimensional nature of fatigue. The patients are instructed to circle a number that describes their present state on a scale of 1 (not at all) to 5 (very much). The response range for each subscale score is 0-28 for the physical and 0-16 for each of the affective and cognitive subscales. The total fatigue score is calculated as the sum of these individual scores. The maximum total score is 60 and the higher scores indicate more severe fatigue.

Physical activity level

Physical activity level (PA) was evaluated with the Japanese version of the International Physical Activity Questionnaire (IPAQ) (long version) [20]. The total PA was expressed in terms of the metabolic equivalent of task/min (MET-min)/day and time spent (in min) for vigorous intensity and moderate intensity PA, as well as hiking, per the IPAQ. Moderate intensity was defined as 4 METs, vigorous intensity as 8 METs, and hiking equivalent to 3.3 METs. The MET-min was calculated by multiplying METs/min participation in PA of moderate and vigorous intensity, as well as hiking. The total PA expressed as MET-min/week was calculated as the sum of the scores and this value was used for analysis.

Statistical analysis

The association between patient characteristics and each outcome measure was compared by the Student's t-test for normalized variables and the Mann-Whitney U test for non-normalized variables. Multiple comparisons were performed using one-way analysis of variance for normalized variables and the Kruskal-Wallis test for non-normalized variables. The association between HRQOL and each outcome measure was compared using the Pearson product-moment correlation coefficient for normalized variables and the Spearman's rank correlation coefficient for non-normalized variables. Multiple logistic regression analysis was performed to adjust for all possible confounders, which were selected based on p value <.05 recorded by the above tests.

All statistical analyses were performed with the JMP software, version 8.0.1 (SAS Institute Japan, Tokyo, Japan). A p value < .05 was considered statistically significant.

Results

Patient characteristics of the 32 participants in this study are shown in Table 1 and the measures of physical function, HRQOL, depression, fatigue, and PA in Table 2. The handgrip strength was 35.0 ± 8.2 kg for men and 20.6 ± 4.2 kg for women. The isometric knee extension strength was 221.8 ± 86.1 N for men and 133.8 ± 29.6 N for women. Of the SF-36 subscales that evaluate HRQOL, the PCS, PF, RP, GH, SF, and RE scores were lower than the Japanese NBS of 50. No significant association was observed between patient characteristics and each outcome measure.

The correlation coefficients between the HRQOL and each outcome measure are shown in Table 3. Regarding the association between physical function and HRQOL, we observed a significant association between the chair stand test and PCS, the 6MWT/chair stand test and PF and between the 6MWT/chair stand test and BP. With regard to the association between HRQOL and depression/fatigue, the MCS, GH, VT, RE, and MH subscale scores were significantly associated with depression, physical, affective, cognitive, and total fatigue. The PCS, PF, and SF scores were significantly associated with depression, physical, affective, and total fatigue. The PA was not significantly associated with the HRQOL.

Results of multiple logistic regression analysis are shown in Table 4. The PCS score was significantly associated with depression and affective fatigue and the PF score was significantly associated with chair stand test and depression. The MCS, RP, VT, and SF scores were significantly associated with depression.

Discussion

In the present study, we investigated the association between physical function and the HRQOL in survivors of hematological malignancies undergoing HSCT.

Table 1. Patient characteristics

Variables		(n = 32)
Mean age, years (SD)		50.8 (11.9)
Sex, male (%)		19 (59.4)
BMI, kg/m ² (SD)		21.6 (2.5)
Primary diagnosis at HSCT (%)	AML	10 (31.3)
	ALL	6 (18.8)
	CML	2 (6.3)
	MDS	1 (3.1)
	MM	2 (6.3)
	NHL	8 (25.0)
	HL	1 (3.1)
Graft type (%)	Autologous	9 (28.1)
	Allogeneic	23 (71.9)
Donor type (%)	BM	14 (43.8)
	PBSC	6 (18.8)
	UCB	12 (37.5)
Conditioning regimen (%)	Myeloablative	23 (71.9)
	non-myeloablative	9 (28.1)
Duration from HSCT (%)	< 1 year	9 (28.1)
	1 - 2 years	7 (21.9)
	> 2 years	16 (50.0)

BMI: Body Mass Index; HSCT: hematopoietic stem cell transplantation; AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; BM: bone marrow; PBSC: peripheral blood stem cell; UCB: umbilical cord blood; SD: standard deviation

Table 2. Physical function, HRQOL, depression, fatigue, and physical activity level in HSCT survivors

Variables		(n = 32)
Handgrip strength, kg (SD)		29.2 (9.8)
Isometric knee extension strength, N (SD)		182.7 (80.1)
6MWT, m (SD)		430.0 (56.7)
Chair stand test, sec. (SD)		9.2 (2.02)
SF-36, points (SD)	PCS	41.3 (14.0)
	MCS	54.0 (7.9)
	PF	43.3 (13.3)
	RP	43.0 (15.2)
	BP	50.9 (9.8)
	GH	48.4 (8.8)
	VT	51.2 (10.5)
	SF	45.8 (14.4)
	RE	48.1 (12.8)
SDS, points (SD)		37.6 (8.6)
CFS, points (SD)	Total fatigue	15.0 (10.0)
	Physical fatigue	6.0 (5.9)
	Affective fatigue	5.5 (3.0)
	Cognitive fatigue	3.5 (3.4)
IPAQ, Mets.min/week (SD)		6,730.1 (16,245.1)

6MWT: 6-minute walk test; SF-36: the MOS 36-Item Short-Form Health Survey; PCS: physical component summary; MCS: mental component summary; PF: physical functioning; RP: physical role functioning; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: emotional role functioning; MH: mental health; SDS: Self-Rating Depression Scale; CFS: Cancer Fatigue Scale; IPAQ: the International Physical Activity Questionnaire; SD: standard deviation

With regard to physical function, Morishita, *et al.* [21] reported that the mean handgrip strength was 21.0 kg, the mean knee extension strength was 204.0 N, and the mean 6MWT result was 425.4 m at discharge in patients undergoing HSCT. In contrast, previous studies that investigated healthy volunteers in their 50s reported that the mean

Table 3. Correlation coefficients between HRQOL and each outcome measure

Variables	PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH	
Handgrip strength	0.22	-0.05	0.19	0.25	0.20	0.03	-0.15	0.25	0.17	-0.02	
Isometric knee extension strength	0.36	-0.05	0.30	0.36	0.15	0.22	-0.02	0.24	0.38	0.10	
6MWT	0.31	0.12	0.48*	0.14	0.41	0.37	0.29	0.17	0.19	-0.01	
Chair stand test	-0.43*	-0.21	-0.67*	-0.29	-0.50*	-0.31	-0.21	-0.36	-0.08	-0.06	
SDS	-0.69*	-0.78*	-0.55*	-0.61*	-0.58*	-0.66*	-0.72*	-0.74*	-0.56*	-0.68*	
CFS	Total fatigue	-0.49*	-0.61*	-0.47*	-0.51*	-0.54*	-0.50*	-0.68*	-0.45*	-0.65*	-0.59*
	Physical fatigue	-0.58*	-0.43*	-0.42*	-0.62*	-0.65*	-0.38*	-0.58*	-0.39*	-0.72*	-0.55*
	Affective fatigue	-0.38*	-0.57*	-0.47*	-0.32	-0.33	-0.39*	-0.61*	-0.50*	-0.41*	-0.45*
	Cognitive fatigue	-0.31	-0.40*	-0.33*	-0.33	-0.28	-0.37*	-0.45*	-0.31*	-0.41*	-0.38*
IPAQ	0.24	-0.03	0.34	0.10	0.15	0.01	0.09	0.09	0.13	-0.15	

* p < 0.05

6MWT: 6-minute walk test; SDS: Self-Rating Depression Scale; CFS: Cancer Fatigue Scale; IPAQ: the International Physical Activity Questionnaire; PCS: physical component summary; MCS: mental component summary; PF: physical functioning; RP: physical role functioning; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: emotional role functioning; MH: mental health

Table 4. Regression coefficient in multiple logistic regression analysis for HRQOL

Variables	PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH	
6MWT	0.02	0.00	0.05	-0.01	0.01	0.04	0.02	-0.02	0.02	-0.01	
Chair stand test	-1.78	0.43	-2.16*	-1.04	-1.36	0.32	0.14	-1.72	0.15	0.26	
SDS	-1.07*	-0.64*	-1.01*	-1.21*	-0.46	-0.54	-0.69*	-2.00*	-0.43	-0.63	
CFS	Physical fatigue	-0.80	0.27	-0.18	-1.05	-0.62	0.09	-0.29	1.51	-1.16	-0.30
	Affective fatigue	1.66*	-0.09	0.99	1.88	0.84	-0.03	-0.10	2.14	0.31	0.23
	Cognitive fatigue	-0.53	-0.70	-0.35	-0.41	-0.33	-0.83	-0.60	-1.21	-0.89	-0.45

* p < 0.05

6MWT: 6-minute walk test; SDS: Self-Rating Depression Scale; CFS: Cancer Fatigue Scale; PCS: physical component summary; MCS: mental component summary; PF: physical functioning; RP: physical role functioning; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: emotional role functioning; MH: mental health

hand grip strength was 45 kg for men and 28 kg for women, and the mean knee extension strength was 507 N for men and 442 N for women [22,23]. Our study showed that physical function in survivors of hematological malignancies undergoing HSCT was similar to or higher than that observed at discharge in patients undergoing HSCT but was remarkably lower than that observed in healthy volunteers.

Regarding the HRQOL, the PCS, PF, RP, GH, SF, and RE (nearly 50% of the subscales evaluated) scores were lower than those recorded by the Japanese NBS. Kisch, *et al.* [3] reported that emotional well-being improved 100 days after HSCT, whereas all other dimensions including the overall HRQOL (assessed with the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation tool showed deterioration. Moreover, physical and social/family well-being scores decreased at the 12-month follow-up, whereas the emotional well-being scores showed improvement. Mitchell, *et al.* [24] reported that compared to the MH scores, the PCS and other scores were significantly lower than the NBS in patients undergoing HSCT who developed chronic GVHD and survived >100 days. These reports prove that the HRQOL in survivors of hematological malignancies undergoing HSCT remained low for prolonged periods after transplantation and that the physical dimension deteriorated more significantly than the emotional dimension of HRQOL. Our study results concur with those reported by the aforementioned studies; the HRQOL in survivors of hematological malignancies undergoing HSCT remained low, and PCS scores were lower but MCS scores were higher than the NBS.

The mental aspect of the HRQOL was shown to improve after discharge because patients undergoing HSCT were of the view that radical cure had been achieved, although there is the limitation of which reason this study clarified.

With regard to the factors associated with HRQOL, the PCS score was significantly associated with depression and affective fatigue, the PF score was significantly associated with the chair stand test and

depression, and the MCS, RP, VT, and SF scores were significantly associated with depression. The only physical function parameter that was associated with the HRQOL was the chair stand test. Notably, depression and fatigue rather than physical function were associated with the HRQOL in survivors of hematological malignancies undergoing HSCT.

Morishita, *et al.* [9] reported that diminished handgrip strength and knee extension strength were not associated with PF and SF scores in patients undergoing HSCT. Our study showed that in addition to physical function, depression and fatigue were associated with HRQOL.

The National Comprehensive Cancer Network (NCCN) guidelines recommend aerobic exercise and resistance training to improve fatigue of cancer patients [25]. Moreover, a few systematic reviews and meta-analyses have reported that physical exercise improved HRQOL and reduced fatigue, anxiety, and depression in patients undergoing HSCT [26-28]. Exercise improves physical function and HRQOL and reduces fatigue and depression; therefore, positive rehabilitation after discharge is useful in survivors of hematological malignancies undergoing HSCT. Early introduction of a rehabilitation program including physical exercise and vocational counseling is important to facilitate early return to work in survivors undergoing HSCT. A study performed by De Boer, *et al.* [29] reported that rehabilitation intervention, such as vocational counseling combined with patient education and biofeedback-assisted behavioral training or physical exercise, achieved higher return-to-work rates in cancer patients.

The limitations of this study are as follows: (a) This cross-sectional study included a small number of patients; therefore, we could not definitively establish causality between physical function and the HRQOL. (b) Transplantation-induced symptoms and patients' living environment are known to be associated with HRQOL; however, these variables were not evaluated in this study. Therefore, further studies that consider these points are warranted.

Conclusion

This study highlights that physical function and the HRQOL were diminished in survivors of hematological malignancies undergoing HSCT and that physical function, depression, and fatigue were significantly associated with the HRQOL in these survivors undergoing HSCT.

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Declaration of Interest statement

Declaration of interest

None.

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