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Importance of Monitoring Physical Function for Quality of Life Assessments in Hematopoietic Stem Cell Transplantation Patients: A Prospective Cohort Study

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Abstract. *Background/Aim: Physical function is known to decrease after hematopoietic stem cell transplantation (HSCT), with the most substantial impairment noted at 90 days post-transplantation. Little is known about the natural course of physical function during the acute post-transplant period preciously. The aim of the study was to monitor the changes in physical function through serial evaluations of the physical function, and identify the effect of physical function on QoL during the acute post-transplant period. Patients and Methods: This prospective cohort study included 41 patients admitted for planned autologous or allogeneic HSCT. Physical impairment was evaluated with decrease in the de Morton Mobility Index (DEMMI) every week and defined as a DEMMI score of more than 2 points after HSCT. The outcome variables for QoL included visual analogue scale (VAS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and Zung Self-rating Depression Scale (SDS) at enrollment and discharge. Results: Based on DEMMI scores, 24.40% of all HSCT patients showed physical impairment, for whom the DEMMI score showed an overall decrease during hospitalization with significant differences in scores at 1, 2, and 3 weeks after HSCT, between 1 week before and 3 weeks after HSCT, and between 1 and 3 weeks after HSCT. There was no significant difference of VAS between admission and discharge between the groups. Each functional subscale of EORTC QLQ-C30 differed significantly between the groups, with lower scores in the physical impairment group. There was only a significant difference in SDS at discharge between the groups. QoL pre-transplantation can be a predictive factor for physical impairment during the acute post-transplant period, which can be detected in the early period after HSCT. Conclusion: Patients during acute post-transplant period had physical impairment and QoL of pre-transplantation was considered a predictive factor for physical impairment. The physical impairment can be detected in the early period after HSCT. Therefore, monitoring of standardized functional outcome measures is important to prevent physical impairment following HSCT.*

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Hematopoietic stem cell transplantation (HSCT) is considered an effective treatment for hematologic and lymphoid cancers, which reduces morbidity and increases the life expectancy of patients. Currently, approximately 50,000 people are treated with HSCT annually, which has substantially increased survival rates (1, 2). Despite these clear benefits, HSCT is also associated with physical (*e.g.*, reduced strength, fatigue, and diminished cardiovascular function) and psychological (*e.g.*, depression, anxiety, stress, and reduced self-esteem) consequences, which adversely influence quality of life (QoL) (3).

Physical function is known to decrease after HSCT, with the most substantial impairment noted at 90 days post-transplantation, and pre-transplantation levels of functioning tend to return within 1 year (4, 5). However, little is known

about the natural course of physical function during the acute post-transplantation period. During this short period, patients have to remain hospitalized and their immune function is extremely low. This results in manifestations of various acute symptoms such as fever and decreased oral intake, which, in conjunction with poor hygiene and decreased physical activity, result in a poor condition for these patients.

Thus, it has been suggested that physical exercise intervention could be beneficial for improving physical function in HSCT patients, especially during the acute post-transplant period. Physical function can be evaluated through various methods, which are mainly classified into the following three aspects: aerobic capacity, muscle strength, and functional capacity (6). Functional capacity is usually evaluated using the 6-min walk test, 50-foot walking time, repeated sit-to-stand movement, Karnofsky Performance Status (KPS), Eastern Cooperative Oncology Group (ECOG) scale, and questionnaires. However, these methods are insufficient to reliably measure the entire physical function of a patient, and can be somewhat subjective and non-specific. Therefore, determining the natural course of physical function during the acute post-transplant period require a reliable method of assessment. The De Morton Mobility Index (DEMMI) has been used for evaluation of physical function in the intensive care unit; however, its applicability during recovery of HSCT has not yet been evaluated. Moreover, it is important to determine the degree to which physical function ultimately affects QoL.

Accordingly, the aim of the present study was to monitor the changes in physical function through serial evaluations of the DEMMI, and identify the effect of physical function on QoL during the acute post-transplant period.

Patients and Methods

Study design and patients. This was a prospective cohort study involving patients admitted for planned autologous or allogeneic HSCT at Hospital from August 2016 to May 2017. The inclusion criteria were: i) 18 years or older and ii) planning autologous or allogeneic HSCT. The exclusion criteria were: i) patients with end-stage cancer or in terminal care, and ii) a severe systemic condition resulting in disability preventing physical examination or exercise. A total of 41 HSCT patients were ultimately included after providing informed consent. This study was approved by the Institutional Review Board of hospital and was conducted according to the Declaration of Helsinki, following Good Clinical Practice guidelines.

Hematopoietic stem cell transplantation (HSCT). The procedure of HSCT in this hospital follows the conventional method (7). The regimen preceding transplantation was designed to eradicate the patient's underlying disease, and then to severely immunosuppress the patient so as to prevent rejection of the transplanted hematopoietic stem cells. For allogeneic HSCT, the conditioning regimen involved the combination of busulfan, fludarabine, and anti-thymocyte globulin or busulfan and cyclophosphamide, and a calcineurin inhibitor and/or methotrexate were used as prophylaxis against graft-*versus*-host disease. For autologous HSCT, a high dose of melphalan was used for patients with multiple myeloma, while a busulfan and melphalan-containing regimen was used for patients with a high risk or relapsed/refractory lymphoma as preparative regimens. Allogeneic or autologous hematopoietic stem cells were harvested by peripheral mobilization, and infused under close monitoring in a specific HSCT ward equipped with HEPA-filtered rooms. Patients were discharged after confirming the implantation safely using bone marrow aspiration and were not followed up for this study.

Table I. *General patient characteristics*.

	Good PF (Mean±SD)	Impaired PF (Mean±SD)	*p*-Value
Subjects (n)	31	10	
Age (year)	47.87±14.44	50.96±13.55	0.501
Gender			
Female	13	5	0.724
Male	18	5	
Type of Cancer (n)			0.791
Multiple myeloma	8	3	
Lymphoma	7	4	
Myelodysplastic syndrome	8	1	
Acute myeloid leukemia	5	1	
Acute lymphoblastic leukemia	1	1	
Acute biphenotype leukemia	1	0	
Rhabdomyosarcoma	1	0	
Type of HSCT (n)			0.469
Autograft	13	6	
Allograft	18	4	
Previous chemotherapy (times)	6.71±5.84	7.30±3.16	0.200
Complete remission (n)	16	4	0.703
Radiotherapy (n)	3	1	1.000
Rehabilitation treatment (n)	1	4	0.009

Age and previous chemotherapy were analyzed with the Mann-Whitney test. Gender, type of cancer, type of HSCT, complete remission, radiotherapy, and rehabilitation treatment were analyzed with Fisher's exact test.

Monitoring of physical function and rehabilitation treatment. The DEMMI score for physical function was determined by physiatrists and trained physical therapists on admission and then every week until discharge. Rehabilitation treatment was performed for patients who i) had physical impairment after transplantation or ii) were not able to ambulate or sit up themselves after HSCT, with the patient's consent. Rehabilitation treatment mainly targeted the patient's disability according to the specific DEMMI score for each patient, including a balance exercise in sitting and standing position, gait training exercise, endurance-oriented exercise, and muscle strengthening exercise in the gym or at bedside for 30 min a day and 3 times a week.

Outcome variables. Clinical data were collected from the medical records of the patients, including hematopoietic cancer type, bone marrow transplantation type, history of chemotherapy or radiation

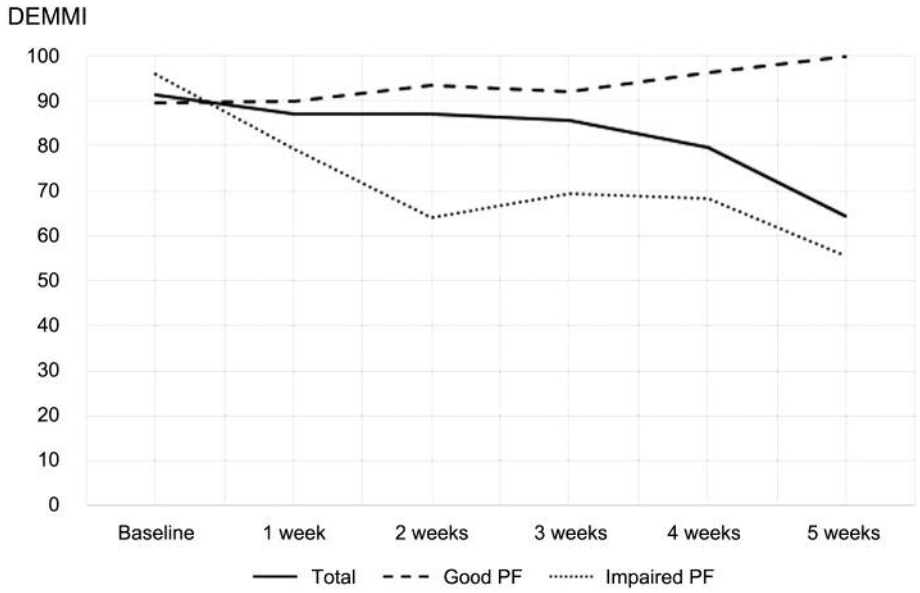

Figure 1. *DEMMI scores as a measurement of physical function after HSCT. The impaired physical function group showed a decreased DEMMI score after 1 week, which significantly decreased from the baseline after 2 weeks ($p<0.05$).*

therapy, and state of complete remission. In addition, laboratory variables, including complete blood count, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, and albumin, were collected at the starting day of HSCT (D0) and 1 week after HSCT (D7).

The DEMMI score is an advanced, reliable, and practical tool for measuring mobility across the spectrum of conditions, from a patient that is bed-bound to one with independent mobility (8). The score is a composite of 15-items, unidimensional measure of mobility on a scale from 0 to 100. A raw ordinal DEMMI score out of 19 is first evaluated for the patient and then converted to an interval-level DEMMI score out of 100 using a conversion table (9). The minimal clinically important difference of the raw ordinal DEMMI score of 2-3 points has been proposed for an adult inpatient rehabilitation population (9); thus, in the present study, a decrease in 2 points was used as the criterion for classifying patients within the physical impairment group (Impaired PF), and those with a decrease of less than 2 points were classified in the no physical impairment group (Good PF).

The outcome variables for QoL determination included the visual analogue scale (VAS), European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), and Zung Self-rating Depression Scale (SDS). The VAS involves assessment of variations in the intensity of pain on a scale from 0 to 10. The EORTC QLQ-C30 was designed to assess the health-related QoL of cancer patients participating in international clinical trials, composed of both multi-item scales and single-item measures (10), and was validated with the Korean version (11). For the present evaluation, in the EORTC QLQ-C30, we used functional scales, including physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. All scores were evaluated on a scale of 0 to 100, and a high score for a functional scale represented a high/healthy level of functioning (10). The Zung SDS is a measurement of clinical severity in depression validated with the Korean version (12), in which a high score represents severe depression. All of these outcomes were assessed through the patients' self-reported assessments conducted at both enrollment and discharge.

Statistical analysis. Descriptive analysis was performed for clinical demographic data of the patients. The Mann-Whitney *U*-test for continuous variables, and Fisher's exact tests according to the expected frequencies for categorical variables were performed to compare the clinical demographic characteristics of the patients with and without physical impairment after HSCT.

The paired *t*-test or Wilcoxon signed-rank test was used to analyze the DEMMI score within a group according to time (week). In addition, the Mann-Whitney *U*-test was performed to compare the amount of change in the DEMMI score over each week between patients that received autologous and allogeneic HSCT. QoL variables and laboratory variables were analyzed with Mann-Whitney *U*-tests. SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical procedures. A p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics. The mean age of all patients was 48.63±14.12 years, and 43.90% of the patients were female (Table I). The most common cancer types were multiple myeloma (26.83%) and lymphoma (26.83%), with equal distributions among patients that received allogeneic and autologous transplants. Patients received 2.12±1.35

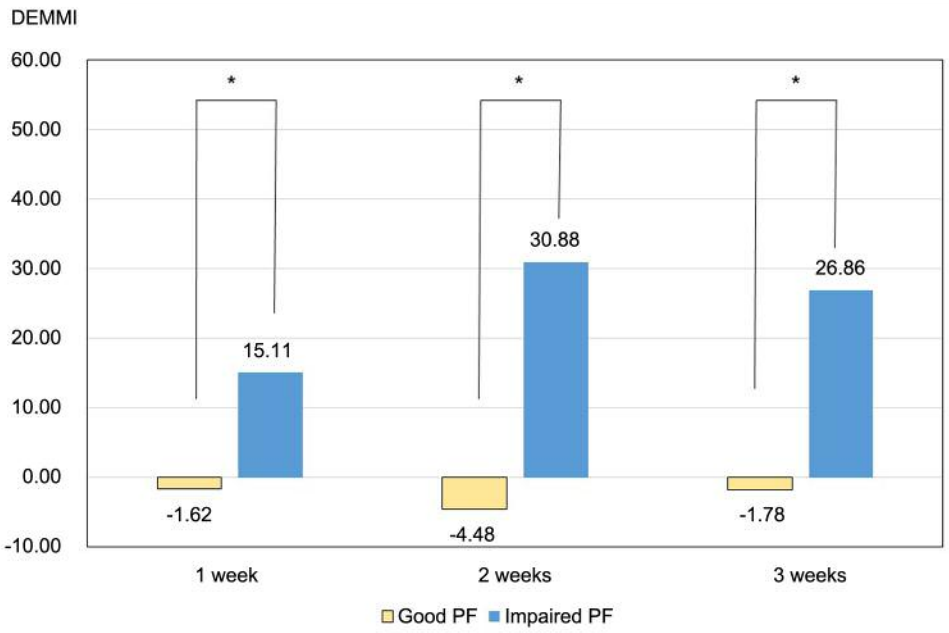

Figure 2. *Decrement of DEMMI scores in both groups after HSCT. Compared with the good physical function group, the impaired physical function group showed a decreased DEMMI score after 1 week ($p<0.05$).*

chemotherapy lines, and 6.85±5.28 bouts of chemotherapy before HSCT, and only 20 patients (54.05%) were in a complete remission state. During hospitalization, five patients (12.20%) received rehabilitation treatment after HSCT according to the criterion.

Monitoring of physical function with HSCT. DEMMI scores, as a measurement of physical function, during the course of hospitalization are summarized in Figure 1. DEMMI scores did not decrease significantly after HSCT; however, the patterns of change clearly differed between the patients with and without physical impairment. Overall, 24.40% of patients showed physical impairment during HSCT. Moreover, the Impaired PF group showed an overall decrease in the DEMMI score during hospitalization for HSCT, whereas no such decrease was detected in the Good PF group. In the Impaired PF group, the DEMMI scores decreased from 96.50±9.02 at baseline to 79.22±17.65 after 1 week and to 64.00±33.89 ($p<0.05$) at 2 weeks after HSCT. For comparison between the groups, the analysis period was limited from baseline before HSCT to 3 weeks after HSCT since the majority of patients were hospitalized for 3 weeks after transplantation (Figure 2). The impaired PF group showed a significant decrease in the DEMMI score from 1 week after HSCT (15.11±16.46) and the differences were further increased over time (30.88±28.28 at 2 weeks and 26.86±16.93 at 3 weeks). Comparing patients with autologous and allogeneic HSCT, there was not significant difference in the change of DEMMI scores over each week.

Effect of physical function on QoL. The outcome variables for QoL were compared between groups with and without physical impairment (Table II). There was no significant difference of VAS at admission and discharge between the groups. However, there were significant differences in functional scales of EORTC QLQ-C30, including physical functioning, emotional functioning, and cognitive functioning at admission, and physical, role, emotional, and cognitive functioning at discharge between the groups, in which the patients with physical impairment had significantly lower scores. In SDS, there was only a significant difference detected between the groups at discharge.

Laboratory findings related with physical function. There were no significant differences in the change of all laboratory variables from D0 to D7 between the groups.

Discussion

The majority of patients who undergo HSCT are generally at normal or near-normal functional levels before the transplantation, but ultimately develop functional deficits post-transplantation owing to summative impairments. These impairments originate from various sources, including the cancer itself, prior cancer treatment, transplant induction, graft-*versus*-host disease, immobility, infection, steroid-related side effects, and other sequelae of transplantation (13-

Table II. *Relation of quality of life with physical impairment.*

	Good PF (N=31)	Impaired PF (N=10)	*p*-Value
VAS			
Admission	2.77±2.07	2.40±1.84	0.643
Discharge	3.29±2.13	4.10±2.33	0.300
EORTC C-30			
Physical functioning			
Admission	72.26±14.92	53.33±19.88	0.006
Discharge	71.40±13.24	45.33±23.89	0.002
Role functioning			
Admission	65.59±26.15	50.00±27.22	0.143
Discharge	67.74±23.15	43.33±31.62	0.039
Emotional functioning			
Admission	72.31±22.09	50.83±32.74	0.036
Discharge	76.08±18.35	58.33±29.92	0.046
Cognitive functioning			
Admission	80.65±14.34	66.67±13.61	0.018
Discharge	82.26±15.48	68.33±18.34	0.042
Social functioning			
Admission	57.53±26.12	48.33±34.65	0.520
Discharge	62.37±23.16	50.00±33.33	0.329
SDS			
Admission	41.39±6.46	47.44±9.37	0.055
Discharge	39.00±6.36	47.70±9.46	0.014

All data were analyzed with the Mann-Whitney test. Values are mean±standard deviation.

16). Cancer-related fatigue has been demonstrated to be one of the most commonly reported side effects associated with cancer and its treatment (17). However, the natural course of physical function during the acute post-transplant period is poorly studied, although intensive cancer therapy and transplantation immediately affect physical function. In the present study, 24.40% of all patients that received HSCT showed physical impairment (according to the DEMMI score) within about 3 weeks after transplantation, and their function significantly decreased as of 1 week after HSCT. Thus, this study suggests that approximately one quarter of HSCT patients can show physical impairment, which can be detected in the early period. In line with these findings, Hacker *et al*. (17) reported that physical activity significantly decreased and fatigue increased at approximately 1 week after HSCT as the acute post-transplant period. In this previous study, physical activity was measured by the Actiwatch score, which involves an activity monitor and a disposable wristband. Together, these findings point to the importance of immediate monitoring and interventions to maintain or increase physical function in patients undergoing HSCT.

In contrast to the scarcity of studies related to physical impairment during the acute post-transplant period, numerous studies have assessed physical impairment during the long term-post-transplant period and rehabilitation in patients that received HSCT (6, 18, 19). These studies generally evaluated physical function using the 6-min walk test, 50-foot walking time, repeated sit-to-stand movement, KPS, the ECOG scale, and questionnaires. However, the 6-min walk test, 50-foot walking time, and repeated sit-to-stand movement are only feasible for patients who can walk and cannot be used in patients with a risk of infection due to a low absolute neutrophil count or hemorrhage after HSCT. Moreover, KPS, ECOG, and questionnaires are somewhat subjective and non-specific, as they are typically evaluated by non-rehabilitation specialists. By contrast, the DEMMI score is widely used in the field of rehabilitation and is assessed by a rehabilitation specialist as physical medicine along with a rehabilitation physician or rehabilitation therapist. Moreover, because this method involves direct observation and specific functional tasks, it is considered to be more objective and helpful for determining the related rehabilitation plan. Despite recognition of the importance of evaluation of physical function in patients with HSCT, no easily administered, standardized, and objective functional outcome measures have been established to date. Therefore, more investigations on standardized functional outcome measures such as the DEMMI score and their application are needed to identify the specific impairments in patients and perform focused and earlier interventions by rehabilitation professionals (13).

The results of the present study pointed to significant differences of QoL at admission between groups with and without physical impairment during the post-transplantation period despite a similar level of physical function between groups at admission. In other words, the pre-transplantation QoL may serve as a useful predictive factor for physical impairment during the acute post-transplantation period. In support of this finding, a previous study demonstrated that physical and mental functioning at 6 months after transplantation was strongly associated with QoL measured at the pre-transplantation stage (20). However, our study further emphasizes that QoL measured at pre-transplantation specifically affects physical function in the early stage post-transplantation, for about 3 weeks after HSCT, as well as long-term functional consequences. Thus, patients with a good QoL are considered to be more likely to define themselves as normal and then adjust their activity level to that of a healthy individual, whereas patients with a poor QoL may adjust to a relatively lower level of activity before the transplantation (20).

We did not find any association between laboratory findings and physical function in the present cohort. Usually liver or kidney function may be related with fatigue, weakness, and decreased activity (21, 22). Considering no relationship between organ and physical function in acute period after HSCT, decreased physical function may be originated from immobilization (23). Immobilization

progresses 8% reductions in cross-sectional area of muscle and 23% reductions in strength by 14 days (24). HSCT patients undergo fever, mucositis, decreased oral intake, or restriction in care unit. This acute ill condition leads the patient to feel lethargy and be immobilized in bed. Decrease activity and immobilization may decrease muscle power and balance which exacerbate immobilization, and finally physical function and performance can be impaired. However, certain biomarkers related with physical function have been identified, such as sex hormones, insulin, leptin, and inflammatory markers, since physical activity might influence menstrual function, as well as reduce insulin resistance and systemic inflammation (25, 26). Thus, further study on the changes of biomarkers during the post-transplantation period is necessary to identify specific impairments and their causes.

Several limitations of this study must be addressed. First, the sample size was quite small and there were missing data for the DEMMI score, which limit the generalizability of these findings. Although it is generally difficult to assess physical function during the acute post-transplantation period, since the patients might be too exhausted to participate in assessments, the advantage of this study is that the physical function was objectively evaluated using the DEMMI score in all patients. Second, we did not evaluate the effects of rehabilitation therapy on physical impairment during the study period because of the small sample size. Therefore, further study is warranted to confirm the present findings and establish a more precise program of rehabilitation therapy during the acute post-transplantation period.

This research focused on monitoring changes of the physical function through the de Morton Mobility Index (DEMMI) score and identifying the effect of physical function on QoL during acute post-transplant period. Patients during acute post-transplant period had physical impairment and QoL of pre-transplantation was considered a predictive factor for physical impairment. The physical impairment can be detected in the early period after HSCT. Therefore, monitoring of standardized functional outcome measures score is important to maintain the physical impairment during HSCT.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendment or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

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Authors' Contributions

Conceptualization: IK, KS; Literature search and analysis: KS, HD, SK; Data extraction: HD, SK; Table drafting: HD, SK; Manuscript editing: IK, KS, YK, JH, DS; Critical revision of the manuscript for important intellectual content: IK, KS, YK, JH, DS; All Authors have read and approved the manuscript.

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