Title

Evaluation of indices for predicting recovery of exercise tolerance in patients surviving allogenic hematopoietic stem cell transplantation

Running title

Indicators for predicting the recovery of exercise tolerance

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Abstract

Purpose: Decline in physical function in the early stage after allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a major challenge. Exercise tolerance tests, such as the 6-minute walk test, are useful markers for predicting exercise tolerance and various other traits, including cardiometabolic risk and non-relapse mortality. This retrospective cohort study aimed to investigate and identify predictors of recovery of exercise tolerance in the early stage after allo-HSCT.

Methods: Ninety-eight patients were classified into recovery and non-recovery groups according to the median 6-minute walk distance (6MWD) at discharge.

Results: Logistic regression analysis revealed that pre-post change in knee extensor strength (ΔKES) and hematopoietic cell transplantation comorbidity index were useful predictors of recovery of exercise tolerance at discharge and moderate predictors of 6MWD recovery in the early post-transplant period. Receiver operating characteristic (ROC) analysis showed that pre-transplant ΔKES was an accurate predictor of 6MWD recovery in the early post-transplant period. The cutoff point for ΔKES calculated using the Youden index was -1.17 Nm/kg.

Conclusions: The results of this study emphasize the importance of the need for programs designed to prevent muscle weakness in the early period after allo-HSCT. The results from markers of recovery of exercise tolerance are promising and can be used for patient education in rehabilitation programs after allo-HSCT.

Keywords

1. hematopoietic stem cell transplantation

2. six-minute walk test

3. knee extensor strength

4. Youden index.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for intractable blood diseases. In recent years, the number of long-term survivors has increased due to the surge in the number of transplants and improved outcomes resulting from the development of supportive care, including conditioning regimens and immunosuppressive agents [1]. As the number of long-term post-transplant survivors increases, the importance of maintaining physical function after allo-HSCT is gradually being recognized [2,3]. In particular, the decline in physical function in the early post-transplant period has been shown to be an important factor affecting the quality of life among long-term post-transplant survivors [4].

The decline in physical function soon after HSCT is a serious issue to be resolved. Specifically, exercise tolerance, which reflects overall physical endurance, has been reported to be reduced in the early post-transplant period (from the start of conditioning to discharge from the hospital) [5,6]. Exercise tolerance in allo-HSCT patients is often assessed using the 6-minute walk test [7,8]. Previous reports have indicated that the 6-minute walk test in the early post-transplant period can predict cardiometabolic risk [9], social reintegration [10], and non-relapse mortality in the late post-transplant period [11], making it a useful marker for predicting not only exercise tolerance but also various other traits. Based on this background, rehabilitation interventions should be performed early after transplantation to control the decline in exercise tolerance that frequently occurs during the transplantation period. In this relation, a certain intervention effect has been demonstrated [12,13].

The abovementioned studies have clarified the changes in exercise tolerance and the effects of rehabilitation after transplantation on outcomes. However, to date, no studies have explored the characteristics of allo-HSCT patients who regained exercise tolerance during the transplantation period or the indicators for predicting early recovery of exercise tolerance after transplantation.

Therefore, this study aimed (i) to clarify the status and characteristics of exercise tolerance in the early stage after allo-HSCT and (ii) to identify useful indices for predicting the recovery of exercise tolerance in the early stage after allo-HSCT. This study presents important data for physicians, nurses, and therapists providing care in the early post-transplant period. It may be useful in planning effective rehabilitation strategies for patients in the early stage after allo-HSCT and may provide useful information for restoring exercise tolerance.

Subjects and methods

Eligibility criteria

A total of 177 patients who underwent allo-HSCT at the Department of Hematology and Oncology in Kyoto University Hospital between June 2010 and February 2019 were enrolled in this study. Patients who died during hospitalization and those with missing evaluations were excluded. Finally, 98 patients were included in this study. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Kyoto University (approval number: R0715). Informed consent was obtained from all participants for their involvement in this study.

Measures

The 6-minute walk test is an assessment method used to evaluate exercise tolerance and has been reported to have high reliability and validity in a variety of areas, including pulmonary diseases and spinal cord injury [14,15]. This test was performed according to the protocol recommended by the American Thoracic Society [16]. Briefly, a flat, easy-to-walk, 30-m long straight track was set up, and the patient walked for 6 min under maximal effort conditions. The patients were instructed in advance to lean against a wall to rest if they needed to take a break while walking. The total distance walked in 6 min (6-minute walk distance [6MWD]), including rests, was adopted as the final walking distance. The 6-minute walk test was evaluated once at each time point. Any cardiac event (e.g., unstable angina, myocardial infarction) within one month prior to the test was considered a contraindication for measurement.

Data collection

The following clinical data were obtained from all patients: sex, age, body mass index (BMI), Eastern Cooperative Oncology Group performance status, hematopoietic cell transplantation comorbidity index (HCT-CI), diagnosis, stem cell source, disease status, conditioning, acute graft-versus-host disease (GVHD), infection, time to neutrophil engraftment, hospitalization period after allo-HSCT, hematological data at discharge (hemoglobin, serum total protein, and albumin), rate of rehabilitation implementation, and knee extensor strength (KES). Data were obtained from the electronic medical record system.

In this study, KES was measured during a 3-s isometric contraction using IsoForce GT-330 (OG Giken Co., Ltd., Okayama, Japan). The force sensor was placed 5 cm above the ankle on the front of the lower leg in a sitting position. We used the higher score (N) obtained from two trials for further analyses. In addition, extension torque was calculated by multiplying force by the lever arm length and was expressed as the ratio of body weight (Nm/kg) [17].

Physical function assessment and rehabilitation protocol

All patients underwent physical function testing in three phases. Each physical function was evaluated before transplantation (i.e., before conditioning), after transplantation (i.e., after engraftment of transplanted stem cells), and at discharge (i.e., on the last day of the rehabilitation program). To assess whether engraftment was successful, the number of neutrophils exceeding $0.5 \times 10^{10}/\mu L$ was determined on three consecutive days, and complete donor chimerism was confirmed through chimerism analysis using a bone marrow sample. Physical functioning was included in the analysis by calculating the degree of change in each period (the change from pre-transplant to post-transplant was expressed as Δpre-post, whereas the change from post-transplant to discharge was presented as Δpost-dis).

All patients underwent rehabilitation interventions during their hospital stay. The detailed rehabilitation programs are described elsewhere [18]. In brief, patients received five rehabilitation sessions per week, which included stretching, resistance training, walking, cycling, and stair climbing. In addition, the hospital met the standards of clean management (ISO standard, class 8), and rehabilitation could be performed in the ward even in the early neutropenic phase after transplantation. After engraftment, the patients started the rehabilitation program in the rehabilitation center, where the interventions mainly focused on improving their physical function and re-acquiring activities of daily living for discharge to home.

Definition of subject grouping

In this study, the median value of 6MWD at the time of hospital discharge was used to classify subjects into the two groups [19,20]. Because the median value of 6MWD at the time of discharge for the subjects of this study was 493 m, the subjects were classified into one group with a 6MWD of 493 m or more at the time of discharge (6MWD recovery group), and a second group with a 6MWD of 493 m or less (6MWD non-recovery group).

Statistical analysis

Statistical analyses were performed using SPSS software version 18.0 (IBM SPSS Inc., Armonk, NY, USA). We considered two-sided $p < 0.05$ as statistically significant. Using the Mann–Whitney *U*-test and unpaired *t*-test, we compared the patients' characteristics between the 6MWD recovery and non-recovery groups. Furthermore, repeated measures analysis of variance (ANOVA) was used to evaluate parameters over time, and post-hoc comparisons were performed using the Tukey method. In addition, we used the univariate simple logistic regression test to calculate the unadjusted odds ratio (OR), 95% confidence interval (CI), and *p* value to determine the correlation between the characteristics during allo-HSCT and 6MWD at discharge. Moreover, multivariate logistic regression analyses with dependent variables (6MWD) were performed using variables with $p < 0.05$ in the univariate analyses and confounding factors such as sex, age, BMI, and 6MWD before HSCT were evaluated. The overall accuracy of the potential variables in predicting 6MWD recovery at discharge was summarized using the area under the receiver operating characteristic (AUROC) curve, and the correlated receiver operating characteristic (ROC) areas under the curve were compared using a nonparametric test. The optimal cutoff point for variables to predict 6MWD recovery at discharge was determined using the Youden index as follows: J = max (sensitivity + specificity - 1) [21].

Results

Patients' characteristics

The median age at the time of allo-HSCT was 46.5 years, and the median BMI was within the normal range in both groups. At the time of transplantation, 63% of patients had complete remission, and 71% of patients received myeloablative conditioning as a pre-transplant condition. The median time of evaluation starting from the day of HSCT was 21 days after implantation and 66.5 days at discharge.

The time to neutrophil engraftment and the rate of rehabilitation implementation were not significantly different between the two groups, and acute GVHD tended to occur in the non-recovery group. Post-transplant hospital stay was significantly shorter in the 6MWD recovery group than in the non-recovery group ($p < 0.05$; Table 1).

Recovery rate of 6MWD

The changes in 6MWD over time during the transplant period are shown in Fig. 1. Two-way ANOVA showed a statistically significant interaction between changes in 6MWD at each time point for each group ($p < 0.05$). The 6MWD at each time point was significantly higher in the 6MWD recovery group than in the non-recovery group (p <

0.01). Both the 6MWD recovery and non-recovery groups showed a significant decrease from pre-transplant to post-transplant and a significant increase from post-transplant to discharge. In the 6MWD recovery group, Δ (pre-post) was -57.7 m and Δ(post-dis) was 70.6 m, whereas in the non-recovery group, Δ (pre-post) was -80.4 m and Δ(post-dis) was 48.4 m. There were no statistically significant differences between the two groups.

Knee extensor strength

The 6MWD recovery group had significantly higher KES at each time point than the non-recovery group ($p < 0.01$), and there was no significant change from pre-transplant to discharge in the 6MWD recovery group. In contrast, KES significantly decreased from pre-transplant to post-transplant in the non-recovery group ($p < 0.01$). With regard to the degree of change in KES, a significant difference in Δ(pre-post) was observed between the two groups, and the decline from pre-transplant to engraftment day was greater in the non-recovery group ($p < 0.05$) (Fig. 2).

Factors predicting recovery of 6MWD

Univariate analysis revealed that sex, BMI, HCT-CI, hemoglobin, pre-transplant KES, and ΔKES (pre-post) were associated with 6MWD recovery at discharge (Table 2). A multivariate analysis using the variables extracted from the univariate analysis identified elevated HCT-CI (OR, 0.09; 95% CI, 0.01-0.54; $p = 0.01$) and ΔKES (pre-post) (per 0.5 Nm/kg change; OR, 4.29; 95% CI, 1.72-10.26; $p = 0.001$) as significant risk factors for predicting 6MWD recovery at discharge (Table 2).

The ROC analysis showed that change in KES from pre-transplant to engraftment day

(ΔKES pre-post) was an accurate discriminator (AUROC: 0.66, $p = 0.001$), with a cutoff point of -1.17 Nm/kg (sensitivity, 0.78; specificity, 0.40).

Discussion

In this single-center retrospective cohort study on the recovery of exercise tolerance in the early post-transplant period after allo-HSCT, the following two major findings were obtained. (i) A detailed evaluation of exercise tolerance in the early post-transplant period, divided into three periods, showed that in both groups, 6MWD decreased from pre-transplant to post-transplant and showed a tendency for recovery from post-transplant to discharge. Likewise, in patients whose 6MWD recovery was above the median at discharge, the pre-transplant 6MWD was also at a high level. (ii) ΔKES (pre-post) (AUROC: 0.66, $p = 0.001$), and HCT-CI were found to be predictors of early post-transplant exercise tolerance at discharge and also moderate predictors of early post-transplant 6MWD recovery [22].

To the best of our knowledge, this is the first study to investigate in detail the changes in exercise tolerance during the early post-transplant period and also the first to identify factors that influence the recovery of exercise tolerance, further suggesting the importance of early post-transplant rehabilitation to achieve early recovery of exercise tolerance after allo-HSCT.

The discovery of useful discriminatory items for predicting the recovery of exercise tolerance after allo-HSCT is crucial to provide appropriate and clear goals of rehabilitation for patients scheduled for transplant and those who underwent transplantation. In this study, we identified useful discriminatory indices for 6MWD recovery in the early post-transplant period through logistic regression analysis and determined the cutoff point using the Youden index. The results indicated that when KES decreased by more than -1.17 Nm/kg in the period from pre-transplant to neutrophil engraftment (approximately 20 days), exercise tolerance at discharge did not reach pre-transplant levels.

Currently, allo-HSCT patients may experience a considerable decrease in activity even before transplantation due to the effects of chemotherapy and radiotherapy [23,24]. Nevertheless, the importance of pre-transplant rehabilitation is well documented, and previous reports have indicated that pre-transplant rehabilitation is feasible and effective in improving muscle strength and exercise tolerance [25,26]. We also believe that it is important to enhance rehabilitation and improve each physical function prior to the time of transplantation, as the subsequent non-relapse mortality rate has been reported to be increased in patients with a 6MWD of less than 400 m [11]. Furthermore, the change in 6MWD decreased from pre-transplant to post-transplant and subsequently recovered at discharge, suggesting that if the physical function before transplant is high, the 6MWD at discharge may improve to a high level.

In contrast, elevated pre-transplant HCT-CI was identified as a factor limiting 6MWD recovery at discharge. The HCT-CI score is an index that evaluates the pre-transplant general condition and comorbidity; the higher the score, the higher the risk of death after transplant [27]. In addition to increasing the mortality risk of transplantation, elevated HCT-CI at the pre-transplant evaluation may delay the recovery of exercise tolerance in the early post-transplant period, as suggested by the results of this study. In patients with many comorbidities at the time of pre-transplant evaluation, enhancing pre-transplant rehabilitation and improving physical function may reduce the delay in the recovery of exercise tolerance.

After scrutinizing the characteristics of the two groups during the transplant period, ΔKES was identified as a factor affecting 6MWD, especially in the early post-transplant period. KES is known to decrease during the transplant period [28,29], and post-transplant GVHD, in particular, has been reported to exacerbate the decline in physical function [18,30,31]. The 6MWD non-recovery group tended to have a higher incidence of GVHD than the recovery group, and it is possible that such early post-transplant complications affected physical function. The development of rehabilitation strategies to maintain KES, especially during the period between transplantation and engraftment, is considered a current challenge in the field. Although a number of studies have focused on exercise load in patients after allo-HSCT, most of them were conducted in the stable post-transplant period [3]; hence, the setting of exercise load in the early post-transplant period requires further research.

This study had several limitations. First, it was a single-center study with a small sample size. In the future, multicenter studies are necessary. Second, although the study provided a marker and cutoff points to predict early recovery of exercise tolerance after transplantation, it did not provide effective rehabilitation strategies for allo-HSCT patients with loss of exercise tolerance. At least in the period from pre-transplant to post-transplant, when the loss of exercise tolerance and muscle strength is the most severe, it is necessary to consider non-traditional rehabilitation methods, which will continue to be a major challenge.

In conclusion, ΔKES (pre-post) and HCT-CI are factors that can predict the recovery of 6MWD early after transplantation, and patients with a ΔKES (pre-post) of more than -1.17 Nm/kg are more likely to not achieve 6MWD recovery at discharge. The indices identified in this study were found to predict the recovery of exercise tolerance during the transplant period. We believe that these indices have provided encouraging results that can be used for patient education in rehabilitation programs.

Declarations

Funding: Not applicable.

Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Ethics approval: All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Kyoto University Institutional Review Board (approval number: R0715).

Consent to participate: All subjects signed an informed consent to participate in this study.

Consent for publication: All subjects signed an informed consent for the publication of this report.

Code Availability: Not applicable.

Availability of data and material: The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: Conceptualization: [Ryota Hamada, Tadakazu Kondo, Kazuhiro Harada, and Masanobu Murao]; Methodology: [Ryota Hamada, Tadakazu Kondo, Kazuhiro Harada, and Masanobu Murao]; Formal analysis and investigation: [Ryota Hamada, Tadakazu Kondo, and Masanobu Murao]; Writing-original draft preparation: [Ryota Hamada, Tadakazu Kondo, and Masanobu Murao]; Writing-review and editing: [Tadakazu Kondo, Kazuhiro Harada, Masanobu Murao, Junsuke Miyasaka, Michiko Yoshida, Honami Yonezawa, and Manabu Nankaku]; Supervision: [Manabu Nankaku, Yasuyuki Arai, Junya Kanda, Akifumi Takaori-Kondo, Ryosuke Ikeguchi, and Shuichi Matsuda].

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Figures

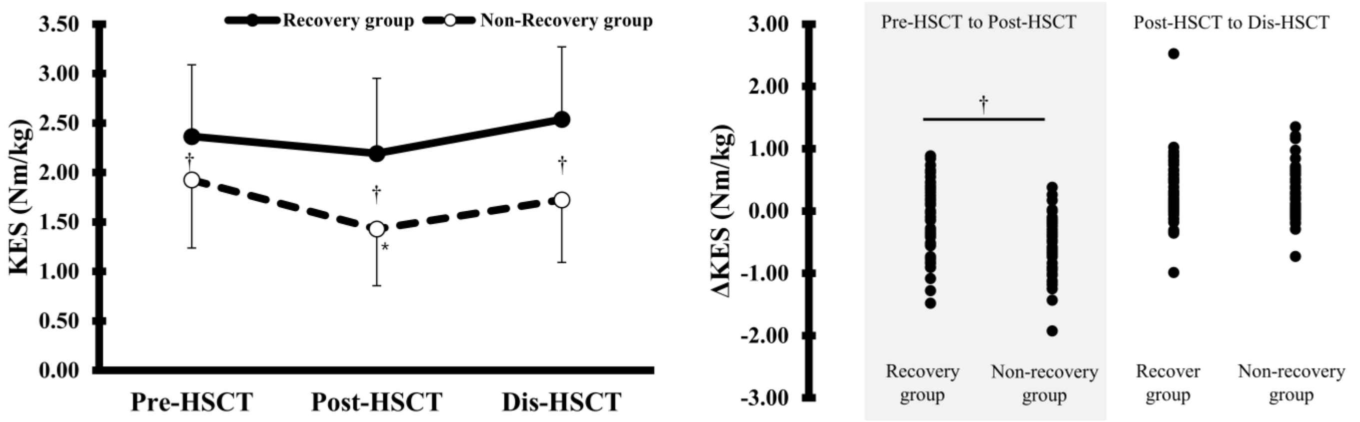

Fig 1. Changes in 6MWD from pre-transplant to discharge

* Significant difference compared with each period.

† Significant difference between the groups.

Abbreviations: Dis, discharge; 6MWD, 6-minute walking distance.

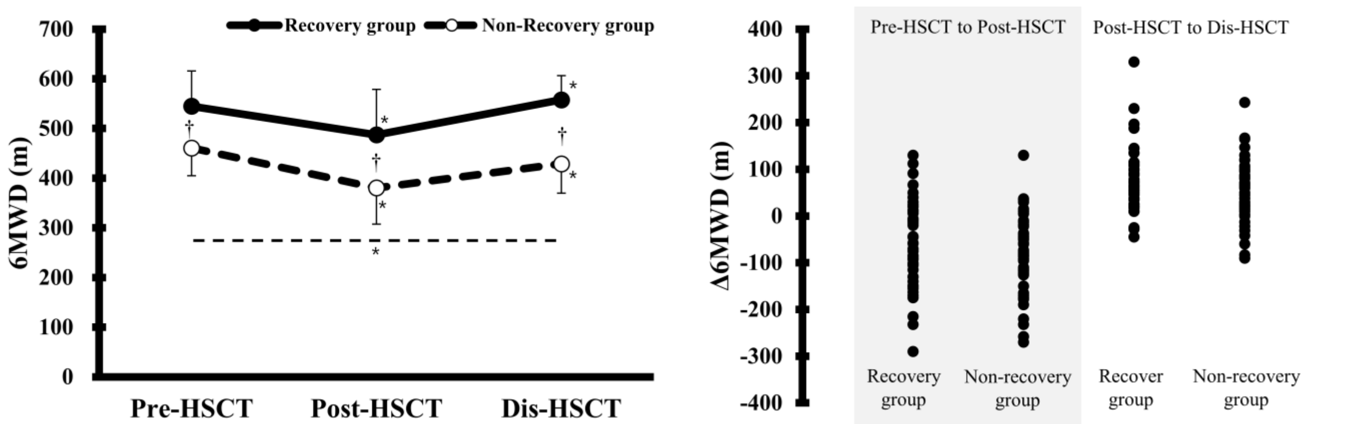

Fig 2. Changes in KES from pre-transplant to discharge

* Significant difference compared with each period.

† Significant difference between the groups.

Abbreviations: Dis, discharge; KES, knee extensor strength.

Tables

Table 1. Patient background and treatment during hospitalization

Variables		Total	Recovery of 6MWD at discharge		*P*
		N = 98	Y (N = 49)	N (N = 49)	
Pre-HSCT characteristics					
Sex	Male/Female	62 (63%)/36 (37%)	37 (76%)/12 (24%)	25 (51%)/24 (49%)	0.02*
Age	median (range)	46.5 (17-68)	46.0 (18-68)	47.0 (17-66)	0.41
BMI	mean (range)	21.7 (15.1-33.2)	22.0 (16.0-28.6)	21.4 (15.1-33.2)	0.42
PS	0-1/2-4	93 (95%)/5 (5%)	48 (98%)/1 (2%)	44 (90%)/5 (10%)	0.15
HCT-CI	0-1/2-	78 (80%)/20 (20%)	43 (88%)/6 (12%)	32 (65%)/17 (35%)	0.07
Diagnosis	AML	38 (39%)	18 (37%)	21 (43%)	0.97
	MDS	19 (19%)	9 (18%)	10 (20%)	
	ALL	25 (26%)	12 (25%)	11 (23%)	
	ML	16 (16%)	10 (20%)	7 (14%)	
Stem cell source	Rel-BM	9 (9%)	4 (8%)	5 (10%)	0.97
	Rel-PB	12 (12%)	6 (12%)	6 (12%)	
	UR-BM	44 (45%)	21 (43%)	24 (49%)	
	CB	33 (34%)	18 (37%)	14 (29%)	
Disease status	CR/nCR	62 (63%)/36 (37%)	34 (70%)/15 (30%)	28 (57%)/21 (43%)	0.21
Conditioning	MAC/RIC	70 (71%)/28 (29%)	32 (65%)/17 (35%)	38 (78%)/11 (22%)	0.18
Post-HSCT characteristics					
Infection	- / +	77 (79%)/21 (21%)	37 (76%)/12 (24%)	40 (82%)/9 (18%)	0.62
aGVHD	all/Gr2-4	64 (65%)/34 (35%)	25 (51%)/24 (49%)	30 (61%)/19 (39%)	0.41
Neut engraft, d	median (range)	21.0 (19.0-48.0)	21.0 (19.0-48.0)	21.0 (12.0-48.0)	0.53
Rehabilitation implementation rate, %	median (range)	83 (47-100)	86 (55-100)	82 (47-100)	0.77
Variables at discharge					
Hospitalized period, d	median (range)	43 (32-126)	62 (32-109)	72 (33-126)	0.02*
Hgb, g/dl	mean (range)	9.3 (6.8-14.7)	9.6 (6.8-14.7)	9.0 (7.0-13.0)	0.08
TP, g/dl	mean (range)	5.8 (3.6-7.0)	5.8 (3.6-6.9)	5.8 (4.3-7.0)	0.76
Alb, g/dl	mean (range)	3.6 (2.6-4.8)	3.7 (2.9-4.8)	3.6 (2.6-4.8)	0.24

Abbreviations: Y, yes; N, no; HSCT, hematopoietic stem cell transplantation, BMI, body mass index; PS, performance status; CT-CI, hematopoietic cell transplantation comorbidity index, AML; acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; ML, malignant lymphoma; Rel, related; UR, unrelated; BM, bone marrow; PB, peripheral blood; CB, cord blood; CR, complete remission; nCR, nonCR; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; aGVHD, acute graft-versus-host disease; Gr, grade; Neut, neutrophil; engraft, engraftment; Hgb, hemoglobin; TP, serum total protein; and Alb, serum albumin.

Table 2. Uni-and multi-variate analyses of patients' factors affecting recovery of 6-minute walk distance at discharge

Variables		Univariate		Multivariate	
		OR (95%CI)	*p*	OR (95%CI)	*p*
Control variable					
Sex	Female	0.33 (0.14-0.79)	0.01*	0.73 (0.15-3.52)	0.69
Age	40 y or over	0.66 (0.27-1.61)	0.37	2.26 (0.42-12.1)	0.34
BMI	< mean	2.99 (1.31-6.82)	0.009*	2.34 (0.53-10.02)	0.26
6MWD before HSCT		1.11 (1.06-1.16)	0.000*	1.13 (1.06-1.21)	0.000*
Independent variable					
Pre- and post-HSCT characteristics					
PS		0.18 (0.02-1.63)	0.12		
HCT-CI	2-	0.25 (0.90-0.71)	0.01*	0.09 (0.01-0.54)	0.01*
Diagnosis	AML	1.00 (reference)			
	MDS	0.87 (0.32-2.39)	0.79		
	ALL	1.12 (0.44-2.85)	0.81		
	ML	1.53 (0.53-4.43)	0.42		
Stem cell source	Rel-BM	1.00 (reference)			
	Rel-PB	1.00 (0.29-3.34)	1		
	UR-BM	1.00 (0.45-2.21)	1		
	CB	1.20 (0.51-2.80)	0.66		
Disease status	nCR	0.58 (0.25-1.34)	0.21		
Conditioning	MAC	1.83 (0.75-4.48)	0.18		
Infection	+	1.44 (0.54- 3.81)	0.46		
aGVHD	Gr2-4	1.83 (0.75-4.48)	0.18		
Neut engraft, d	> median	0.84 (0.38-1.87)	0.68		
Variables at discharge					
Hospitalized period, d	> median	0.47 (0.21-1.06)	0.07		
Hgb, g/dl	< mean	0.43 (0.19-0.98)	0.04*	0.50 (0.11-2.14)	0.35
TP, g/dl	< mean	0.73 (0.32-1.67)	0.46		
Alb, g/dl	< mean	0.51 (0.22-1.15)	0.1		
Evaluation for physical function					
KES before HSCT (per 0.5Nm/kg change)		1.55 (1.14-2.13)	0.005*	1.50 (0.84-2.70)	0.16
ΔKES (per 5% change)		1.80 (1.18-2.76)	0.006*	4.29 (1.79-10.26)	0.001*
Δ6MWD (per 5% change)		1.01 (0.99-1.04)	0.19		

Abbreviations: OR, odds ratio; CI, confidence interval; KES, knee extensor strength; and 6MWD, 6-minute walking distance.

Δ indicates difference between pre- and post-HSCT. Others are shown in Table 1.