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CITATION:

Hamada, Ryota ...[et al]. Intramuscular Adipose Tissue Content Predicts Patient Outcomes after Allogeneic Hematopoietic Stem Cell Transplantation. Transplantation and Cellular Therapy 2022, 28(9): 602.e1-602.e7

ISSUE DATE:

2022-09

URL:

http://hdl.handle.net/2433/276060

ELSEVIER
Transplantation and Cellular Therapy
journal homepage: www.tctjournal.org
ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Supportive Care

Intramuscular Adipose Tissue Content Predicts Patient Outcomes after Allogeneic Hematopoietic Stem Cell Transplantation

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Article history:
Received 15 April 2022
Accepted 14 June 2022

Keywords:
Rehabilitation
Allogeneic hematopoietic transplantation
CT
Muscle

A B S T R A C T

During clinical courses involving treatment with allogeneic hematopoietic stem cell transplantation (allo-HSCT), multidisciplinary patient assessment including physical function is indispensable, and quantitative skeletal muscle loss is a poor prognostic marker. Deteriorating quality of muscle from intramuscular adipose tissue degeneration can be important as well, because many patients are cachexic or sarcopenic before allo-HSCT, although this approach has not yet been used in such patients. We conducted this retrospective cohort study to evaluate the quality as well as quantity of skeletal muscle using computed tomography (CT) scans. The psoas muscle mass index (PMI) and radiographic density (RD) calculated by cross-sectional area and averaged CT values of the psoas major muscle at the umbilical level were used to determine the quantity and quality of muscle, respectively. A total of 186 adult patients, ranging in age from 17 to 68 years (median, 49 years), were included in this study, with 46 (24.7%) assigned to the lower PMI group and 49 (26.3%) assigned to the lower RD group. Low RD was identified as an independent risk factor for poor overall survival after allo-HSCT (adjusted hazard ratio [HR], 2.54; $P < .01$), whereas PMI was not significant. Decreased RD along with a reduced 6-min walking distance before transplantation were significant factors in increased nonrelapse mortality (HR, 2.69; $P = .01$). This study is the first to suggest the use of a qualitative skeletal muscle index to serve as a prognostic indicator following allo-HSCT. RD should be included in pretransplantation screening parameters, and approaches that include rehabilitation focused on improving both muscle quality and quantity may improve the prognosis of allo-HSCT.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be a curative treatment for hematologic malignancies [1-3]. Thanks to newly developed chemotherapies and other supportive strategies, such as antimicrobials, the overall post-transplantation prognosis has improved drastically [4,5]; however, more multidisciplinary approaches, including appropriate evaluation and intervention for physical and nutritional condition, have yet to be fully developed. Most patients receive multiple courses of intensive chemotherapy before transplantation and as a result are in a cancer cachexia state at the time of transplantation [6]. This can adversely affect physical functions [7-11], and skeletal muscle loss may be more prevalent than currently recognized [12].

Thus, skeletal muscle loss can affect outcomes in cancer patients, and poorer post-transplantation survival has been reported in those with lower pretransplantation skeletal muscle mass [13]. Loss of skeletal muscle is usually evaluated using the psoas muscle mass index (PMI), calculated using the cross-sectional area of the psoas major on computed tomography (CT) images at the umbilical level; however, this estimated mass can be inaccurate, particularly in the presence of a large volume of adipose tissue. Therefore, a method that can distinguish intramuscular adipose tissue from skeletal muscle and can accurately evaluate the quality of muscle is needed. For this reason, evaluation using radiographic density (RD), derived from CT values, has recently attracted attention as a novel indicator of skeletal muscle quality [14]. For instance, a

Financial disclosure: See Acknowledgments on page 602.e6.
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https://doi.org/10.1016/j.jtct.2022.06.011

fluctuation in RD is reportedly a sensitive predictor of postoperative survival in patients undergoing surgery [15].

The significance of the quality of skeletal muscle to the prognosis in patients undergoing allo-HSCT is unclear. If both muscle quality and quantity affect prognosis, then rehabilitation focusing on improving muscle quality may improve post-HSCT outcomes. In the current study, we evaluated skeletal muscle quality using RD and examined its effects on post-transplantation outcomes.

METHODS

Eligibility criteria

The study cohort comprised consecutive adult patients who underwent allo-HSCT at Kyoto University Hospital between April 2010 and April 2020. Patients who did not undergo pretransplantation CT imaging were excluded. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Kyoto University (approval R0715).

Image analyses

All images were acquired using a multidetector CT scanner (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan) with the following settings: collimation, 1 mm; scan time, 500 ms; 120 kV peak (kVp); and auto exposure control. Routine calibration of the CT scanner was performed using air and water phantoms.

A horizontal section of the psoas major from noncontrast X-ray CT images was acquired at the umbilical level [16,17] up to 3 months before allo-HSCT (Fig. 1). The quantity of skeletal muscle mass was assessed using the PMI as follows. The subfascial tissue of the psoas major was traced manually on the CT image at the umbilical level, and this traced cross-sectional area was measured bilaterally using the AquariusNET server (TeraRecon, San Mateo, CA). The PMI was calculated by normalizing the cross-sectional area to subject height (cm^2/m^2). This procedure was performed independently by 2 therapists.

Skeletal muscle quality was assessed at the same level as the PMI, and averaged CT values (in Hounsfield units) of the psoas major were measured bilaterally and defined as the RD. Low CT values indicate advanced fatty degeneration [18] and low quality. After acquiring PMI and RD data in all patients, those in the lowest quartile (bottom 25%) among the same sex and age groups were assigned to the low PMI and low RD groups.

Statistical analyses

The following parameters were acquired from patient records as candidates for these prognostic factors: sex, age, body mass index, Eastern Cooperative Oncology Group performance status (ECOG-PS), Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), diagnosis, stem cell source, disease status, type of conditioning regimen, occurrence of acute graft-versus-host-disease (aGVHD), 6-min walking distance (6MWD), as well as PMI and RD.

Patient characteristics were compared using the Mann-Whitney *U* test and unpaired *t* test. Categorical variables were compared using the chi-square test or Fisher exact test. A 2-sided *P* value <.05 was considered statistically significant. Overall survival (OS) was calculated using the Kaplan-Meier method, and differences were assessed using the log-rank test. The cumulative incidence of nonrelapse mortality (NRM) was calculated, treating a relapse as a competing event. The incidence of aGVHD was treated as a time-dependent covariate. Variables that proved significant or borderline significant ($P < .1$) in the univariate analysis were candidates for multivariate Cox regression or Fine-Gray analyses [19]. All statistical analyses were performed using SPSS version 18.0 (IBM, Armonk, NY) and Stata version 17.0 (StataCorp, College Station, TX).

RESULTS

Patient characteristics

A total of 205 allo-HSCT recipients were enrolled in this retrospective cohort study, but 19 of them were excluded because they had not undergone pretransplantation CT imaging at the umbilical level; therefore, 186 patients were included in this study. Patient characteristics and treatment methods are summarized in Table 1. The median time between the initial diagnosis and allo-HSCT was 7 months (range, 2 to 46 months). The median observation period was 36 months, and this value was adopted as the analysis period. The median age at transplantation was 49.0 years (range, 17 to 68 years), and 95% of the patients had a good ECOG-PS (0 to 1). The HCT-CI score was 0 in 75% of the patients. aGVHD was observed in 55% of the whole cohort. Two patients underwent allo-HSCT from an HLA-haploidentical donor.

Evaluations of skeletal muscle quantity and quality

In this study, the reliability of muscle measurements in this study was evaluated with the intraclass correlation coefficient (ICC), and acceptable reproducibility was confirmed for both PMI and RD. The intraexaminer reliability of PMI and RD was .997 (95% confidence interval [CI], .96 to .99) and .943 (95% CI, .74 to .99), respectively, for examiner A and .987 (95% CI, .943 to .999) and .946 (95% CI, .757 to .994), respectively, for examiner B. Furthermore, the interexaminer reliability was .955 (95% CI, .64 to .99) for PMI and .967 (95% CI, .48 to .99) for RD. Muscle measurements using already developed CT images were performed within 1 min in each patient. Distributions of PMI and RD are described according to each sex and age group of patients (Fig. 2), because these parameters interact strongly with sex and age [13]. Based on predetermined classification, 46 patients (24.7%) were assigned to the lower PMI group and 49 patients (26.3%) were assigned to the lower RD group. No significant differences in sex or age were noted between the 2 groups (normal versus lower groups of PMI and RD).

OS and NRM after allo-HSCT

We analyzed OS and NRM after allo-HSCT in the entire cohort and in each subgroup according to pretransplantation skeletal muscle status (PMI and RD) using univariate analyses.

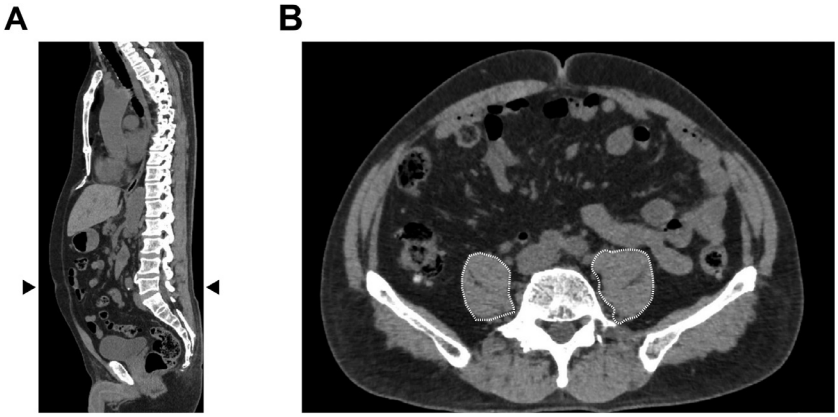

Figure 1. PMI and RD measurement methods. (A) PMI and RD are acquired from CT images at the umbilical level (arrowheads) before allo-HSCT. (B) A sample of a coronal image. Muscle size (PMI) and averaged CT values (RD) in the psoas major muscle (dotted lines) are calculated.

Table 1
Patient characteristics and treatment during hospitalization.

Characteristics			RD Group		*P*
		Total (N = 186)	Normal RD (N = 137)	Lower RD (N = 49)	
Pre-HSCT					
Sex, male/female, n (%)		113 (61)/73 (39)	84 (61)/53 (39)	29 (59)/20 (41)	.79
Age, yr, median (range)		49 (17-68)	48 (20-68)	53 (17-67)	.29
BMI, kg/m^2, median (range)		21.2 (14.4-33.2)	20.8 (15.1-33.2)	21.8 (14.4-31.1)	.31
ECOG-PS, 0-1/2-4, n (%)		176 (95)/10 (5)	131 (96)/6 (4)	45 (92)/4 (8)	.31
HCT-CI, 0-1/2-, n (%)		140 (75)/46 (25)	106 (77)/31 (23)	34 (69)/15 (31)	.27
Diagnosis, n (%)					
	ALL	23 (12)	18 (13)	5 (10)	.89
	AML	64 (35)	48 (35)	16 (33)	
	MDS	38 (20)	28 (20)	10 (20)	
	Others	61 (33)	43 (32)	18 (37)	
Stem cell source, n (%)					
	Rel-BM	16 (9)	12 (8)	4 (8)	.27
	Rel-PB	23 (12)	16 (12)	7 (14)	
	UR-BM	77 (41)	52 (38)	25 (51)	
	CB	70 (38)	57 (42)	13 (27)	
Disease status, CR/nCR, n (%)		117 (63)/69 (37)	88 (64)/49 (36)	29 (59)/20 (41)	.53
Conditioning, MAC/RIC, n (%)		110 (60)/76 (40)	81 (59)/56 (41)	29 (59)/20 (41)	.99
6MWD, m, median (range)		490 (214-694)	500 (230-694)	480 (214-685)	.16
PMI, cm^2/m^2, median (range)		2.73 (.80-6.84)	2.81 (.99-6.84)	2.52 (.80-5.12)	.53
RD, HU, median (range)		44.9 (22.6-67.2)	47.8 (30.2-67.2)	36.4 (22.6-49.6)	<.01
Post-HSCT					
aGVHD, - /+, n (%)		84 (45)/102 (55)	63 (46)/74 (54)	21 (43)/28 (57)	.74

BMI indicates body mass index; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; MDS, myelodysplastic syndromes; Rel, related; UR, unrelated; BM, bone marrow; PB, peripheral blood; CB, cord blood; CR, complete remission; nCR, non-complete remission; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; HU, Hounsfield units.

The lower PMI group showed a tendency toward inferior OS to that of the normal PMI group (HR, 1.68; 95% CI, .91 to 3.11; $P = .09$) (Fig. 3A). In addition, the lower RD group also had significantly lower OS after allo-HSCT compared with the normal RD group (HR, 2.82; 95% CI, 1.60 to 4.97; $P < .01$) (Fig. 3B).

Regarding NRM, no significant difference was observed in the PMI subgroups (lower versus normal; HR, 1.46; 95% CI, .63 to 3.34; $P = .37$) (Fig. 3C), whereas the lower RD group tended toward higher NRM, although the difference was not statistically significant (lower versus normal; HR, 1.91; 95% CI, .86 to 4.21; $P = .10$) (Fig. 3D).

Risk factors for patient prognosis after allo-HSCT

PMI and RD are usually confounded by other patient characteristics. The aforementioned results in univariate analyses were subjected to multivariate analyses, including

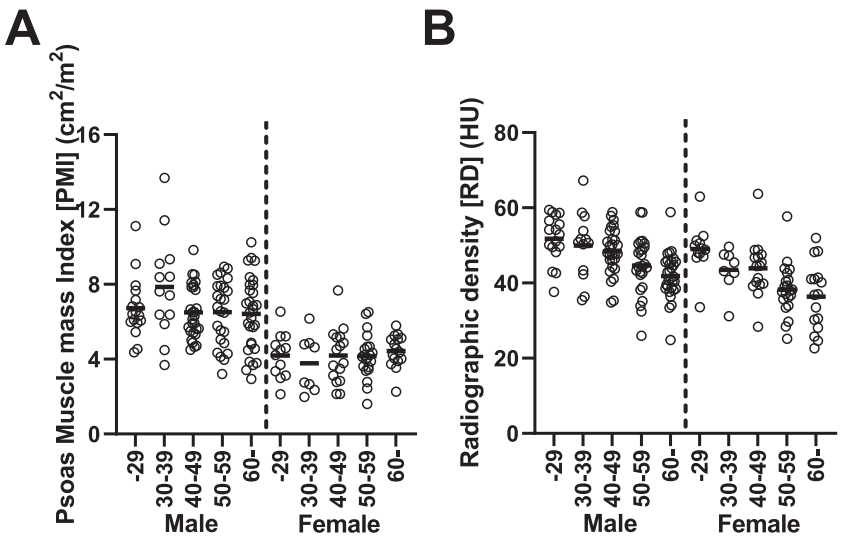

Figure 2. Distribution of PMI and RD by age and sex. Values for PMI and RD are plotted by patient age and sex. White circles indicate individual data, and the horizontal bar indicates mean values in each patient category.

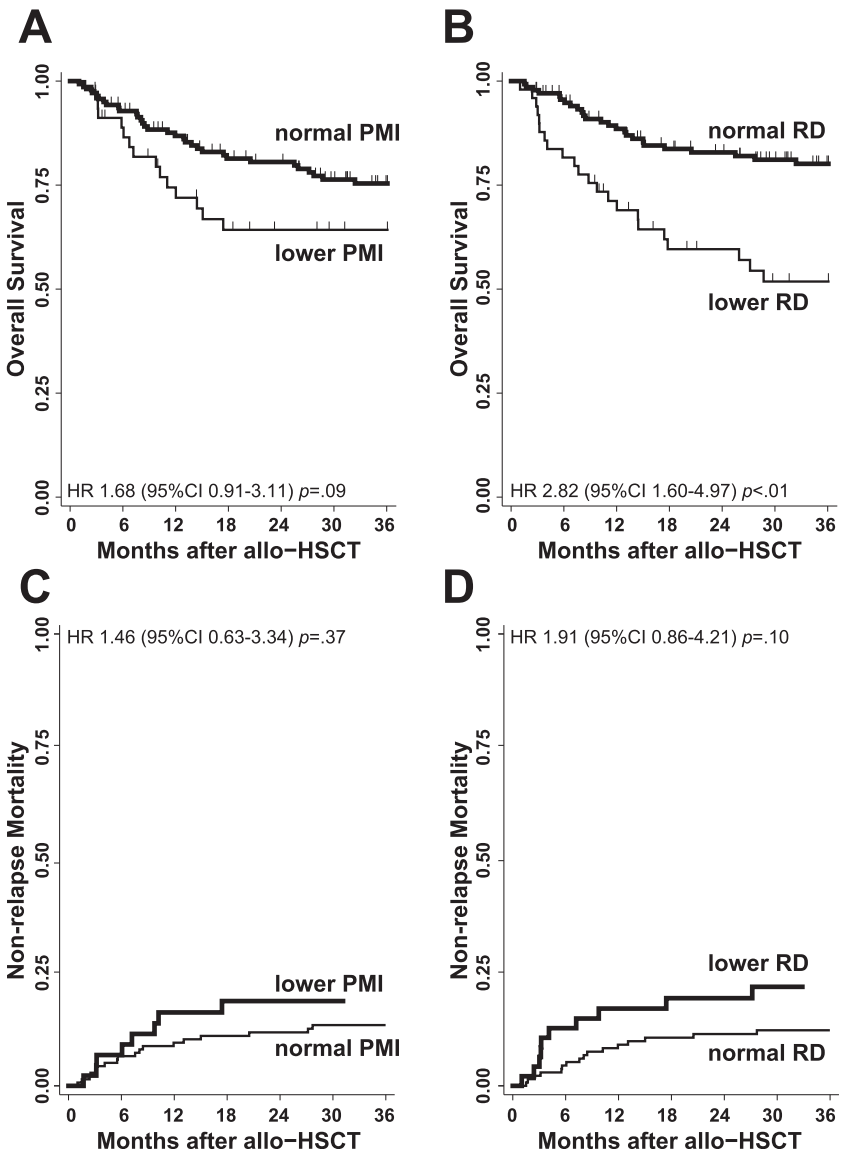

Figure 3. OS (A and B) and NRM (C and D) after allo-HSCT. OS curves are shown according to (A) PMI and (B) RD categories. The cumulative incidence of NRM is also described according to (C) PMI and (D) RD categories. Results from the univariate analyses are also shown.

potential confounding factors (Table 2). Multivariate Cox proportional hazard analyses revealed that higher HCT-CI (HR, 2.30; 95% CI, 1.27 to 4.17; $P < .01$), pretransplantation disease status (HR, 1.81; 95% CI, 1.01 to 3.28; $P = .04$), pretransplantation 6MWD (HR, .97; 95% CI, .96 to .99; $P = .01$), and lower RD (HR, 2.54; 95% CI, 1.42 to 4.51; $P < .01$) were independent risk factors for OS after allo-HSCT (Table 2). PMI was not significant in this analysis (HR, 1.34; 95% CI, .77 to 2.54; $P = .36$).

On the other hand, multivariate analyses for NRM identified higher pretransplantation HCT-CI (HR, 3.35; 95% CI, 1.51 to 7.43; $P < .01$) as an independent risk factor for higher NRM, and neither PMI (HR, 1.13; 95% CI, .49 to 2.60; $P = .76$) nor RD (HR, 1.69; 95% CI, .79 to 3.60; $P = .17$) was significantly associated with NRM (Table 3, Fig. 4A). A reduced 6MWD tended to be associated with higher NRM (HR, .98; 95% CI, .96 to 1.00; $P = .13$). Therefore, we performed an ad hoc analysis and found that the combined decline in both RD and 6MWD (compared with normal RD and 6MWD or either decline in these parameters) is a strong and independent risk factor for NRM (HR, 2.69; 95% CI, 1.05 to 5.75; $P = .01$) (Fig. 4B).

DISCUSSION

This study yielded 2 major findings: (1) lower pretransplantation quality of skeletal muscle (low RD) can be a risk factor for inferior OS following allo-HSCT, and (2) a combined decline in RD and 6MWD is an independent risk factor for higher NRM, and thus we recommend that RD be included in pretransplantation screening parameters. Although there have been several reports focusing on the quantity of skeletal muscle (PMI) in allo-HSCT recipients, this is the first study to provide evidence supporting the use of a qualitative skeletal muscle prognostic index following transplantation. Using it in combination with a muscle index (RD) and physical function test (6WMD) is also a novel strategy.

Previous studies have observed associations between reduced skeletal muscle mass and a higher incidence of post-transplantation aGVHD and an increased risk of death from infection [20], highlighting skeletal muscle status as an

Table 2
Prognostic factors for OS based on univariate and multivariate analyses.

Variable		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
Sex	Female	1.21	.68-2.12	.51			
Age		1.00	.98-1.02	.60			
PS	2-4	2.24	.88-5.66	.08	1.52	.58-3.98	.38
HCT-CI	2-	2.70	1.53-4.76	<.01	2.30	1.27-4.17	<.01
Diagnosis	ALL	1.00	(reference)				
	AML	1.13	.40-3.13	.81			
	MDS	1.43	.49-4.12	.50			
	Others	1.86	.69-5.00	.21			
Stem cell source	Rel-BM	1.00	(reference)				
	Rel-PB	.83	.24-2.87	.77			
	UR-BM	1.44	.55-3.75	.45			
	UR-CB	.57	.19-1.65	.30			
Disease status	nCR	2.11	1.15-3.85	.01	1.81	1.01-3.28	.04
Conditioning	RIC	1.19	.67-2.09	.54			
aGVHD		1.37	.76-2.44	.28			
Pre-HSCT 6MWD		.97	.96-.99	<.01	.97	.96-.99	.01
Pre-HSCT PMI	Low	1.68	.91-3.11	.09	1.34	.71-2.54	.36
Pre-HSCT RD	Low	2.82	1.60-4.97	<.01	2.54	1.42-4.51	<.01

important prognostic marker [12,13]. Sarcopenia, characterized by skeletal muscle loss and reflecting poor nutritional status [21], has been widely reported in association with increased risk and severity of infectious diseases after surgery, and even in patients without specific comorbidities [22]. Thus, the quantity of skeletal muscle is important from a pathophysiologic standpoint, and lower quantity is a prognostic marker of poor outcome post-allo-HSCT.

Quality assessment of muscle is also important, given that intramuscle adipose tissue degeneration is widely expected in patients after several courses of intensive chemotherapy [23] and in aged patients [24]. Our data indicate that muscle quality as assessed by RD can be a marker for long-term prognosis, and that it is more sensitive than the conventionally used muscle quantity marker PMI. This difference in sensitivity can be partially explained from both biological and radiological standpoints. It was recently reported that changes in skeletal muscle quality occur earlier than loss of skeletal muscle quantity [25]. On the other hand, in radiologic measurements of PMI, skeletal muscle with fat accumulation is frequently misclassified as normal skeletal muscle mass [15]. Therefore, an increase in the fat content of skeletal muscle as measured by CT values (RD) can be a more sensitive parameter for evaluating actual muscle function.

Consequently, established quantitative and qualitative muscle parameters should be included in pretransplantation

Table 3
Prognostic factors for NRM Based on univariate and multivariate analyses.

Variable		Univariate Analysis				Multivariate Analysis		
		HR	95% CI	*P*		HR	95% CI	*P*
Sex	Female	.96	.43-2.13	.93				
Age		1.02	.99-1.06	.09		1.01	.98-1.05	.28
PS	2-4	1.48	.34-6.51	.59				
HCT-CI	2-	4.25	1.97-9.18	<.01		3.35	1.51-7.43	<.01
Diagnosis	ALL	1.00	(reference)					
	AML	.97	.59-1.58	.91				
	MDS	1.17	.67-2.04	.57				
	Others	.87	.49-1.54	.63				
Stem cell source	Rel-BM	1.00	(reference)					
	Rel-PB	1.30	.68-2.47	.42				
	UR-BM	1.42	.89-2.27	.13				
	UR-CB	.64	.38-1.07	.12				
Disease status	nCR	2.25	1.04-4.85	.04		1.75	.80-3.81	.15
Conditioning	RIC	1.54	.71-3.32	.26				
aGVHD		1.30	.60-2.82	.50				
Pre-HSCT 6MWD		.98	.96-1.00	.06		.98	.96-1.00	.13
Pre-HSCT PMI	Low	1.46	.63-3.34	.37		1.13	.49-2.60	.76
Pre-HSCT RD	Low	1.91	.86-4.21	.10		1.69	.79-3.60	.17

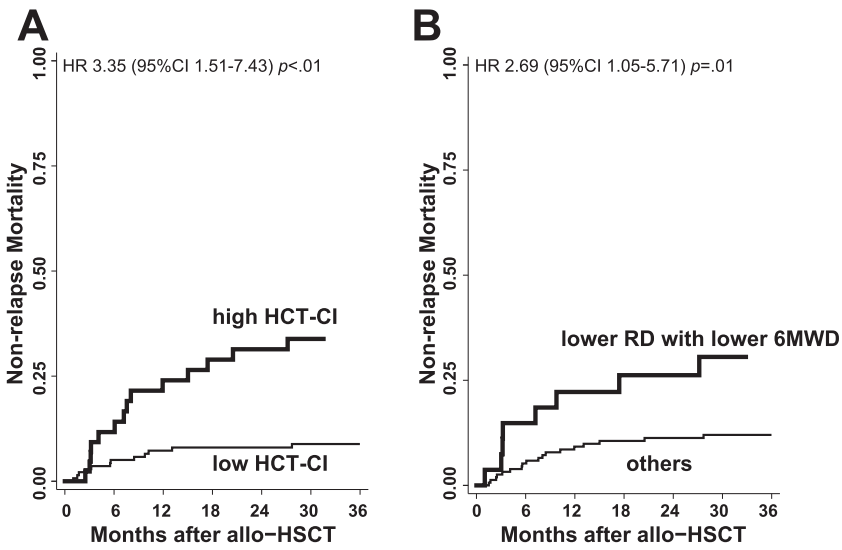

Figure 4. Additional analyses for NRM: cumulative incidence for HCT-CI (A) and the composite subgroup for RD along with 6MWD (B).

comprehensive scoring systems such as HCT-CI. Such scores have not included sensitive parameters of physical functions and may lack the sensitivity to accurately identify individuals who do not have obvious cardiovascular or organ dysfunction [26].

Our analysis is still insufficient to identify the reason for the higher mortality in the lower RD group. Inferior OS in this group is due mainly to higher NRM, and this is related to a higher incidence of post-HSCT infectious episodes (data not shown). In tissues with excess fat accumulation, certain proinflammatory cytokines are constitutively activated, resulting in reduced antigenic response and decreased function of natural killer cells, dendritic cells, and macrophages [27,28] after transplantation, resulting in increased susceptibility to serious infections [29,30]. These immunologic findings partially support our findings, although such analyses are not included in this study.

While decreased muscle quality (indicated by lower RD) is an important parameter in predicting post-transplantation outcomes, this study also proves that the combination with exercise tolerance data yields a more powerful predictor. Increasing attention has been focused on evaluating exercise tolerance in the pretransplantation and post-transplantation periods, as assessed with 6MWD, which has proven to be predictive of post-transplantation cardiometabolic risk [25] and long-term social reintegration [31]. Based on our present results, pretransplantation 6MWD combined with actual muscle quality may be a more comprehensive indicator of skeletal muscle and exercise tolerance. Patients with lower exercise tolerance along with lower muscle quality before transplantation need a strategy for tighter management afterward.

This study reveals a correlation of muscle parameters and prognosis but has several limitations. First, it did not include factors that influence the quality of skeletal muscle before allo-HSCT, such as a history of pretransplantation chemotherapy, nutritional status, decreased activity, and steroid use [32-35]. However, major variables at transplantation are included in the multivariate analyses, and we confirmed that confounding effects on RD were properly adjusted for in the final model. Second, the quantitative and qualitative muscle analyses in this study focused only on the psoas major muscle, not on all skeletal muscle. There is no unified method of assessing systemic skeletal muscle, and our results need to be updated if and when such techniques are developed. However, the psoas major is one of the largest muscles in the human body and is involved in the majority of movements, including gait, and thus can be regarded as representative of all skeletal muscles [36]. Thorough validation is needed in future studies especially for subgroup analyses regarding donor sources.

In conclusion, skeletal muscle assessment before allo-HSCT is useful for discriminating subsequent prognoses following allo-HSCT. In particular, qualitative assessment to analyze intramuscular fat accumulation may be a novel prognostic marker for overall outcomes. Measurements of PMI and RD are quick and easy, and are practical to perform during pre-HSCT screening procedures. Multidisciplinary approaches, including rehabilitation and nutrition, focusing on improving the quality of muscle as well as its quantity, may improve the prognosis of patients undergoing allo-HSCT.

ACKNOWLEDGMENT

The authors thank all medical staff members, including physicians, nurses, laboratory technicians, and therapists, as well as the patients and their family members, for their contributions to this study.

Authorship statement: R.H., T.A., T.K., and M. Murao designed the study, reviewed and analyzed the data, and wrote the manuscript. J.M., M. Matsushita, T.K., and A.O. interpreted the data and revised the manuscript. M.N., Y.A., J.K., R.I., A.TK., R.I., and S.M. contributed to the data collection and critiqued the manuscript. R.H. has full access to the data in the study, and Y.A. and T.K. accept final responsibility for the decision to publish. Y.A. and T.K. contributed equally to this work.

Financial disclosure: This work was supported in part by research funding from the LOTTE Foundation and the Program for the Development of Next-Generation Leading Scientists with Global Insight (L-INSIGHT), sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan (to Y.A.).

DECLARATION OF COMPETING INTEREST

There are no conflicts of interest to report

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