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# Benefit of Reducing Body Weight Loss with A Nutritional Support Pathway in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Data Interpretation D  
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**Background:** This retrospective, historically controlled investigative study examined the benefit of a nutritional support pathway that included nutritional education before the start of conditioning and emphasized oral nutrition in response to nutrition-related adverse events in patients undergoing hematopoietic stem cell transplantation (HSCT).

**Material/Methods:** Participants were patients undergoing allogeneic HSCT; 46 were in the control group (i.e., did not follow our nutritional pathway) and 36 were in the group that underwent nutritional intervention (enhanced nutrition group). We compared the following parameters between groups from the day before the start of conditioning to the day after completion of parenteral nutrition (PN): percent loss of body weight (%LBW), percent loss of skeletal muscle mass (%LSMM), and estimated basal energy expenditure (EBEE) sufficiency rate. The relationship between each parameter and %LBW was also examined. We also compared nutritional indices, gastrointestinal graft versus host disease (GvHD) grade, oral energy intake, and %LBW between groups.

**Results:** There was a relationship between %LBW, %LSMM, and EBEE sufficiency rate in both groups. Compared with the control group, the enhanced nutrition group had significantly improved energy intake amount, EBEE sufficiency rate, PN duration, and oral energy intake over time. The enhanced nutrition group also had increased oral energy intake, no difference in gastrointestinal GvHD grade, and improved %LBW compared with the control group.

**Conclusions:** Use of our nutritional support pathway in patients undergoing HSCT may be beneficial for %LBW and gastrointestinal GvHD grade, enabling early enhanced nutritional intervention after HSCT.

**MeSH Keywords:** **Graft vs. Host Disease • Nutrition Assessment • Nutritional Support • Transplantation, Homologous**

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## Background

Hematopoietic stem cell transplantation (HSCT) can lead to nutrition-related adverse events as a result of reduced body weight [1,2]. In particular, during the period from before the start of conditioning to the marrow suppression period, high levels of chemotherapy and total body irradiation can cause adverse events including vomiting and nausea, low appetite, mucosal defect, and taste defect, and oral intake can become difficult if graft versus host disease (GvHD) develops [3,4]. These adverse events and GvHD may lead to the need for total parenteral nutrition (TPN) [5–7]. Therefore, nutritional support including a discussion on adverse events and gastrointestinal GvHD is needed [8–12].

Improving oral nutritional interventions in patients with cancer has been shown to be associated with a reduction in weight loss and maintenance of quality of life [13,14]. We previously used a nutritional pathway and showed the association between gastrointestinal GvHD and nutrition-related adverse events in patients undergoing HSCT [3,4]. However, the association with weight loss or nutritional adjustments has not yet been adequately evaluated and managing weight loss reduction remains challenging.

We hypothesized that implementing a nutritional pathway for patients undergoing HSCT that included nutritional education before the start of conditioning could reduce weight loss. We then examined the association between nutritional intake and various body composition factors. The purpose of this study was to compare nutrition-related clinical indices between patients who participated in a pilot study (historical control cases) and patients who received a nutritional intervention to increase oral intake, and to evaluate the benefit of our nutritional support pathway in patients undergoing HSCT.

## Material and Methods

### Patients

The Shizuoka Cancer Center Ethics Committee approved this retrospective, historically controlled investigative study (approval number: T24-32). Participants were patients aged 16 to 70 years old with pretreatment performance status (PS) 0-1, who underwent initial HSCT at the Department of Hematology and Stem Cell Transplantation, Shizuoka Cancer Center [15]. Exclusion criteria were parenteral nutrition (PN) period exceeding Day 100 (with the transplantation day as Day 0), organ function not maintained, body mass index (BMI) outside the range 18.5–24.9 kg/m<sup>2</sup>, previous transplantation, patient refusal of nutritional intervention using the nutritional pathway, and participation deemed inappropriate by the physician [16–18].

A total of 166 patients underwent HSCT from January 2007 through October 2016: the historical control group comprised 101 patients who were involved in the pilot study investigating factors related to weight loss from January 2007 through March 2012. The group that underwent nutritional intervention (enhanced nutrition group) comprised 65 patients who were treated from April 2012 through October 2016 and used our nutritional pathway, which included pretreatment education of patients by a nutritionist (Supplementary Figure 1), monitoring of weight loss and nutritional intake during the hospital course, and enhanced oral intake [19,20]. For pretreatment of HSCT, we used myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) [21]. In all patients, the transplantation source included allogeneic peripheral blood stem cell transplantation, cord blood transplantation, and unrelated donor bone marrow transplantation. All participants provided written informed consent.

### Material and Methods

All patients undergoing bone marrow transplantation at the Shizuoka Cancer Center routinely receive any nutritional counseling. The nutritional pathway used by the hematology/stem cell transplant team at the Shizuoka Cancer Center follows the food hygiene protocol in the Hematopoietic Stem Cell Transplant Society Guideline (Supplementary Figure 2) [22–24]. Our nutritional support is composed of regular cuisine and food items and does not use enhanced nutrition or immunonutrition such as glutamine and arginine [25]. In our HSCT nutritional pathway, a nutritionist visits the patient at the bedside every day from before the start of conditioning to completion of PN and inquires about the patient's preferences and adverse events, reports to the physician the energy and protein intakes from both PN and oral nutrition, confirms the physician's orders for dietary adjustment, and applies dietary changes in real time (Supplementary Figures 1, 3) [3,4,26].

We compared the following parameters between the control group and enhanced nutrition group (Supplementary Figures 1, 3) from the day before the start of conditioning (T1: baseline) to the day after PN completion (T2). At T1, we evaluated BMI and percentage of the ideal body weight (%LBW). From T1 to T2, we compared the following variables between groups: %LBW; number of cases with high %LBW ( $\geq 7.5\%$ ) over 3 months; skeletal muscle mass (whole body and trunk and limb mass); and total body fat. In addition, the percent loss of skeletal muscle mass (%LSMM) and percent loss of fat mass (%LFM) were calculated and their relationships to %LBW were compared in each group [27]. Measurements were taken 2 hours after breakfast, from 10 am to 12 pm. We set the reference extracellular fluid to total body fluid ratio as 0.35, and extracellular water to total body water ratio as 0.40. We set the upper limits of extracellular fluid/total body fluid ratio

and extracellular water/body water ratio, indicating mild edema, as 0.35–0.38 and 0.40–0.43, respectively. If edema was noted, the measurements were performed again the next day, as edema may influence lean body mass. All variables were measured using the high-precision body composition analyzer In Body S20® (InBody Co., Ltd., Seoul, South Korea), which uses bioelectrical impedance analysis. The reduction rate for each variable was calculated [28,29]. The energy and protein amounts for daily total nutritional intake, PN intake, and oral intake were calculated. The energy intake sufficiency rate was calculated using the following equation: [(PN calories, orally ingested calories, or enhanced nutrition calories)/total energy intake]×100. We compared the estimated basal energy expenditure (EBEE) sufficiency rate per ideal body weight (IBW) as determined by the Harris-Benedict method for total energy intake during the study period and evaluated the relation to %LBW in both groups [30,31]. The EBEE sufficiency rate was calculated using the following equation: [total energy intake sufficiency/EBEE IBW]×100. IBW was calculated using the following equation: height<sup>2</sup>×22. Oral energy intake as a percentage of EBEE per day at T2 was compared, and the relation to %LBW was evaluated in both groups. We compared the oral energy intake/IBW/day over time in the 2 groups at T2.

To evaluate toxicity during the study period, we examined the relationship over time of the nutrition-related adverse event severity score and PS. The nutrition-related adverse event severity score was defined as the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 and 4.0 total score, in which 1 point is defined as grade ≥1 vomiting and grade ≥2 nausea, low appetite, mucosal defect, and taste defect, divided by the number of cases for that day using information from medical records [32]. PS was defined as the PS divided by the number of cases for all patients each day. To examine symptoms that resolved over time, we divided the total daily severity score for each nutrition-related adverse event by the number of subjects and presented this as a cumulative graph, then added PS to assess as a time-series graph. We compared the incidence of acute GvHD (grade ≥1) and grade of skin, liver, and gastrointestinal GvHD during the study period using the Transplant Registry Unified Management Program [33]. We divided the gastrointestinal GvHD cases in both groups into grade 0 and grade ≥1, and compared their relation to EBEE sufficiency rate and %LBW. We evaluated the relation between gastrointestinal GvHD (grades 0–4) and oral energy intake/IBW/day in the 2 groups. We then compared the duration of PN administration during the study period and oral energy intake/IBW/day in each group. In addition to the nutrition-related indices, we also investigated the exact day of neutrophil engraftment, defined as the first of 3 consecutive days when an absolute neutrophil count ≥500/cm<sup>3</sup> was achieved with no decline thereafter. We also examined serum albumin (Alb) and C-reactive protein (CRP) levels prior to pretreatment (during the 2 weeks

before T1), as well as the day of their maximum values of these parameters during the clinical course, and evaluated the relationship between these 2 laboratory values. We compared the nutritional status of these 2 groups: MAC and RIC [34].

### Statistical analysis

All data are reported as medians (range). The Wilcoxon signed-rank test was used to compare the 2 groups. Spearman's rank-order correlation was used to analyze the relationship between nutrition-related adverse event severity score over time and PS. JMP version 12.0 for Windows (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis, and statistical significance was defined as  $P < 0.05$ .

## Results

From January 2007 through October 2016, 166 patients underwent HSCT. Of these patients, 101 were in the control group and 65 were in the enhanced nutrition group. In the control group, 22 patients had a BMI outside of the range 18.5–24.9 kg/m<sup>2</sup> at T1, and 33 patients deviated from the nutritional pathway (29 transplantation-related deaths and 4 receiving PN exceeding Day 100 due to GvHD or other reasons). In the enhanced nutrition group, 17 patients had a BMI outside the range 18.5–24.9 kg/m<sup>2</sup> at T1, and 12 patients deviated from the nutritional pathway (5 transplantation-related deaths and 7 receiving PN exceeding Day 100 due to GvHD or other reasons). The remaining 46 patients in the control group and 36 patients in the enhanced nutrition group were included in the analysis.

Baseline characteristics are shown in Table 1. No differences were found in sex, median age, pretreatment regimen, or transplant source between the 2 groups. Table 1 shows the characteristics of patients in the 2 groups during the assessment period. No differences were found in BMI or %IBW between the 2 groups at T1. A significant difference was found between the groups in duration of PN. Compared with the control group, the enhanced nutrition group had significantly improved %LBW and %LSMM as well as significantly fewer cases of high %LBW of ≥7.5% over 3 months. The %LBW and %LSMM were related in both groups, but not %LFM (Figure 1A, 1B).

In terms of the nutrition-related indices, a significant difference was found between the control group and enhanced nutrition group in total calorie intake. No significant differences between groups were seen in PN calorie intake and PN protein intake (Table 2). No difference was found in the oral intake initiation day or PN calorie intake ratio between the two groups. The enhanced nutrition group had a significantly increased EBEE sufficiency rate. %LBW and EBEE sufficiency rate

**Table 1.** Characteristics of patients.

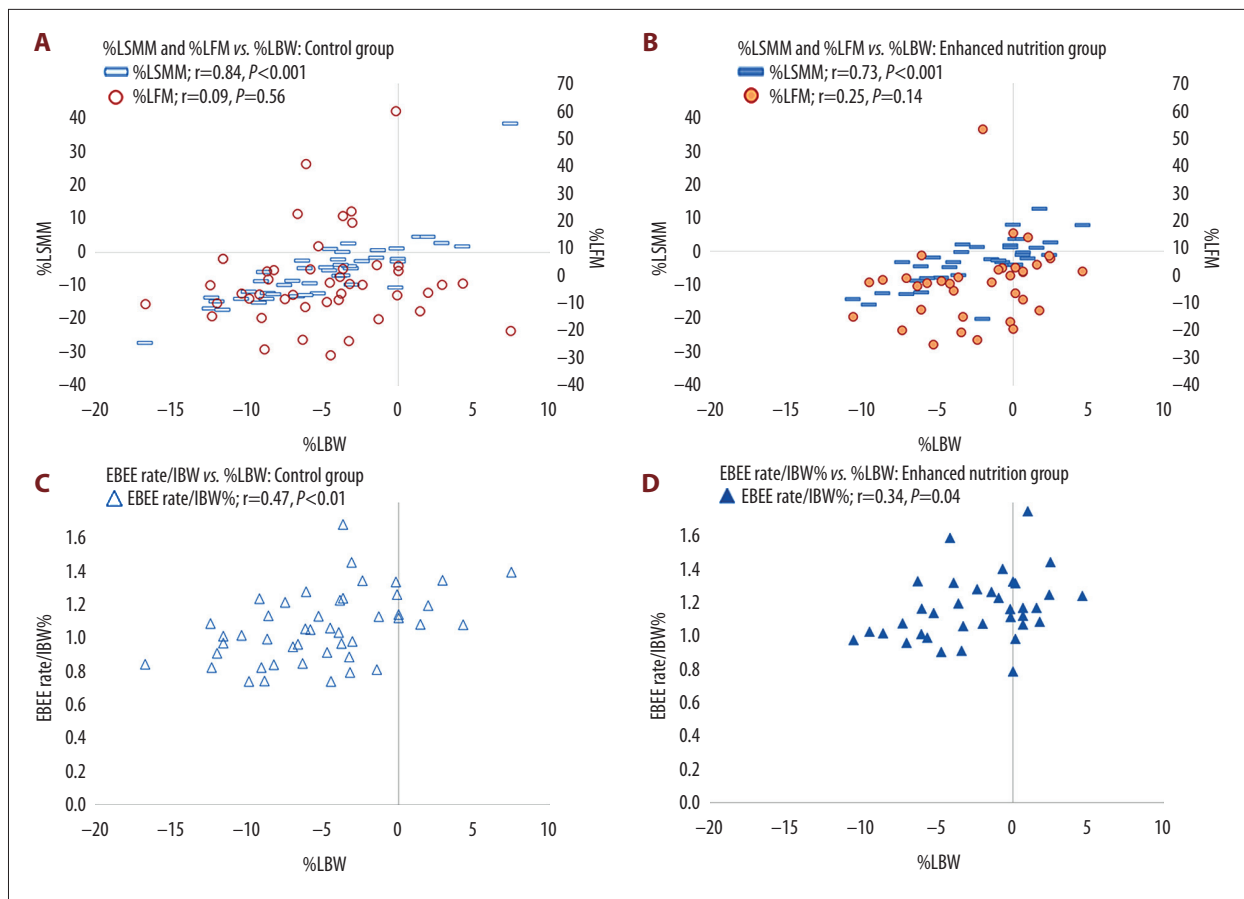
	Control group	Enhanced nutrition group	P
Study period	2007.04–2012.12	2013.01–2016.12	
Sample size, n (Male/Female)	46 (34/12)	36 (20/16)	0.0819
Age, mean (range)	54 (17–68)	60 (27–70)	0.0394
Disease			
Acute myeloid leukemia	14	11	
Myelodysplastic syndrome	13	6	
Chronic myeloid leukemia	3	1	0.4412
Acute lymphoblastic leukemia	10	7	
Malignant lymphoma	5	9	
Multiple myeloma	1	2	
Conditioning regimen			
MAC	33	27	
Busulfan (>6.4 mg/kg)	17	16	
TBI ≤5Gy in a single fraction, 8Gy in multiple fractions)	13	9	
Melphalan (>140 mg/m <sup>2</sup> )	3	2	
RIC	13	9	0.741
Busulfan (≤6.4 mg/kg)	2	0	
TBI (<5Gy in a single fraction, <8Gy in multiple fractions)	0	3	
Melphalan (≤140 mg/m <sup>2</sup> )	11	6	
Transplant source			
Peripheral blood stem cell transplantation	13	5	
Unrelated bone marrow transplantation	28	25	0.2677
Cord blood transplantation	5	6	
Cases of %LBW ≥7.5% (n)	15	3	0.0141
Days on parental nutrition, n (range)	62 (29–100)	53 (34–92)	0.0372

MAC – meloablative conditioning; TBI – total body irradiation; RIC – reduced-intensity conditioning; %LBW – percent loss of body weight. *P* value is before versus after assessment period (Mann-Whitney test or chi-square test).

were related in both groups (Figure 1C, 1D). Compared with the control group, the enhanced nutrition group had a significantly improved daily oral energy intake EBEE sufficiency rate at T2 (Table 2) and significantly improved oral energy intake/IBW/day over time (Figure 2). PN duration (the assessment duration) and oral energy intake/IBW/day were related in both groups (Figure 3A, 3B). The nutrition-related adverse event severity score and PS showed a direct relationship over time in both groups (Figure 4).

No significant differences were found between groups in the incidence rate of GvHD grade ≥1. Compared with the control group, the enhanced nutrition group had a significantly higher skin GvHD grade, but no difference in grade was found in liver or gastrointestinal GvHD. No difference was found in gastrointestinal GvHD grade between the control group (grade 0, 29; grade 1, 15; grade 2, 1; grade 3, 1) and the enhanced nutrition group (grade 0, 26; grade 1, 9; grade 2, 1; grade 3, 0; *P*=0.6902). After dividing the gastrointestinal GvHD cases in each group by grade 0 and grade ≥1, %LBW was significantly

lower in grade ≥1 patients than in grade 0 patients in the control group, but no such difference in %LBW was found in the enhanced nutrition group (Table 3). A relationship was found between gastrointestinal GvHD grade (grades 0–3) and oral energy intake/IBW/day in the control group but not in the enhanced nutrition group (Figure 3C, 3D). Engraftment day was significantly earlier in the control group than in the enhanced nutrition group (Day 17 versus Day 19; *P*=0.0438). Both groups showed a significant difference in both Alb and CRP levels prior to pretreatment and peri-engraftment (control group: Alb Day 14, CRP Day 12; enhanced nutrition group: Alb Day 15, CRP Day 12), but no relationship was found between the differences in the 2 groups (Figure 5). No significant differences were found between groups in the nutritional status of MAC and RIC (Table 4).

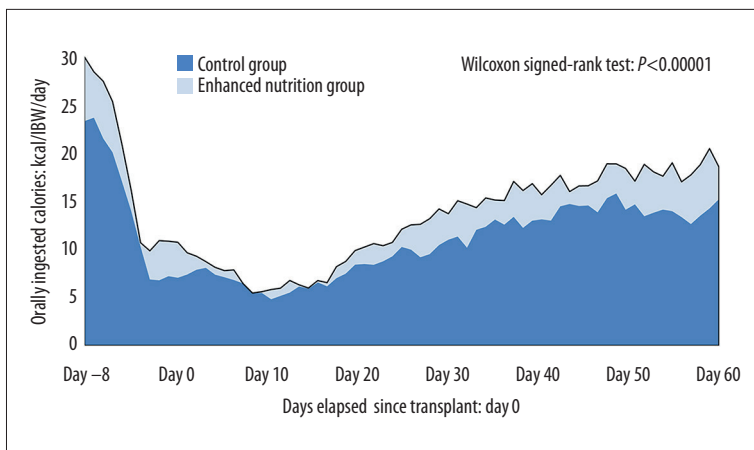


**Figure 1.** Relationship between percent loss of body weight, percent loss of skeletal muscle mass, and percent loss of body fat in the control group and the enhanced nutrition group (A, B). Relationship between percent loss of body weight and basal energy expenditure sufficiency rate (C, D). LBW – loss body weight; LSMM – loss of skeletal muscle mass; LFM – loss of fat mass; EBEE – estimated basal energy expenditure; IBW – ideal body weight.

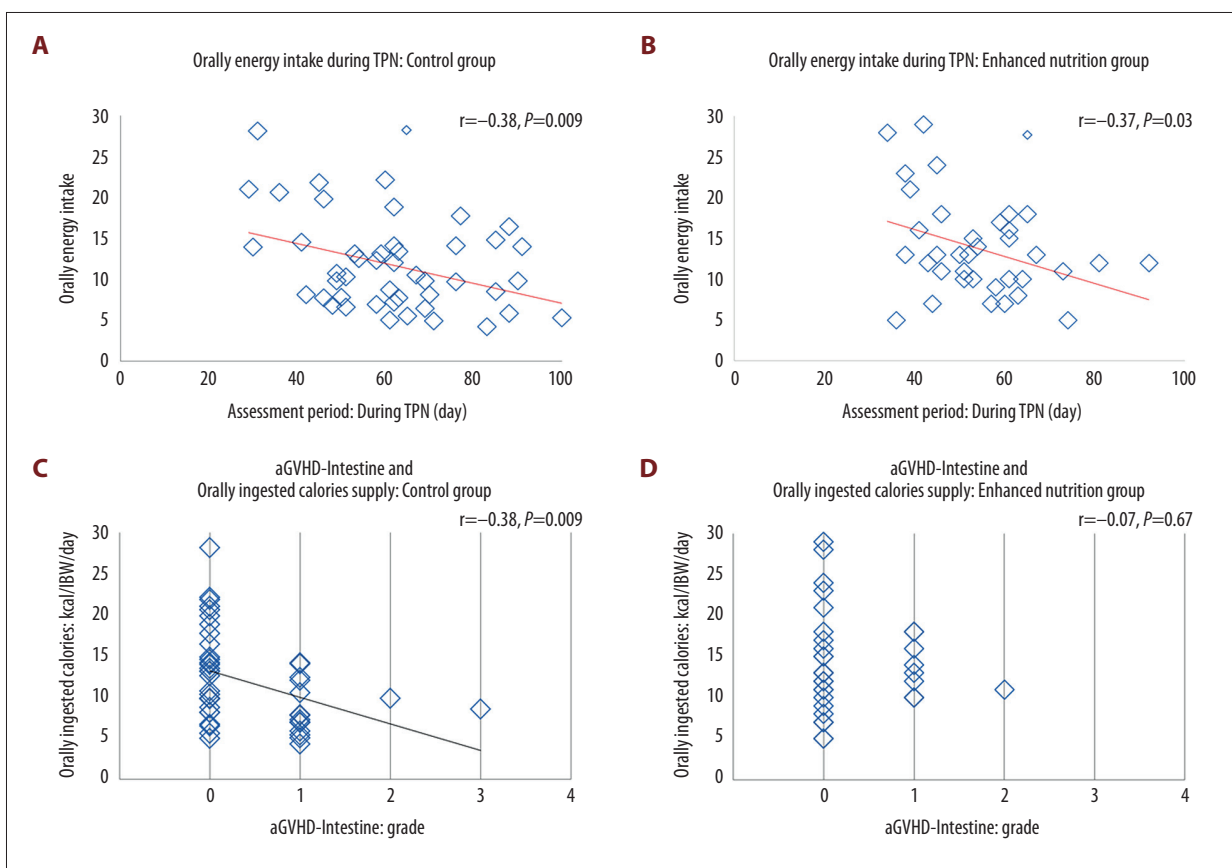
**Table 2.** Assessment results in the control group and enhanced nutrition group.

	Control group	Enhanced nutrition group	P
Total calorie intake (range)	24 kcal/IBW/day (17–36)	26 kcal/IBW/day (19–38)	0.0386
PN calorie intake (range)	13 kcal/IBW/day (0–32)	13 kcal/IBW/day (0–18)	0.8611
Orally ingested calories (range)	10 kcal/IBW/day (4–28)	13 kcal/IBW/day (5–29)	0.0977
Total protein intake (range)	0.7 g/IBW/day (0.5–1.3)	0.9 g/IBW/day (0.6–1.3)	0.0062
PN protein intake (range)	0.4 g/IBW/day (0.0–1.0)	0.5 g/IBW/day (0.0–0.6)	0.1865
Orally ingested protein intake (range)	0.3 g/IBW/day (0.1–1.1)	0.4 g/IBW/day (0.2–1.1)	0.0699
Oral intake initiation day (range)	Day 14 (0–53)	Day 16 (0–41)	0.7974
PN energy rate (range)	57% (0–88)	51% (0–78)	0.1959
EBEE rate/IBW% (range)	104% (73–167)	115% (79–175)	0.021
Daily oral energy intake EBEE sufficiency rate at T2 (range)	94% (30–140)	106% (55–183)	0.0159

EBEE – estimated basal energy expenditure; IBW – ideal body weight; PN – parenteral nutrition; T2 – the day after PN completion. P value is before versus after assessment period (Mann-Whitney test or chi-square test).



**Figure 2.** Oral energy intake over time in each group.



**Figure 3.** Relationship between total parenteral nutrition (TPN) period and oral energy intake in each group (A, B). Relationship between gastrointestinal graft versus host disease (GvHD) and oral energy intake in each group (C, D).

**Discussion**

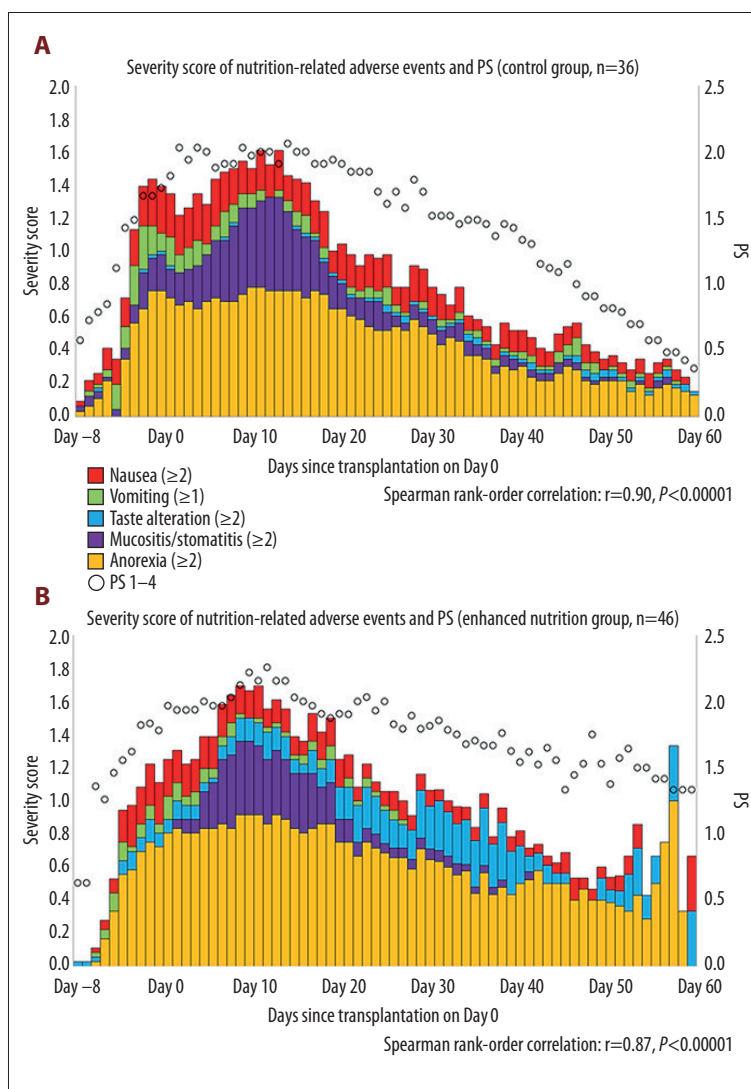
This study used various nutritional indices to investigate the reduction in body weight loss in patients who underwent HSCT with or without an enhanced nutritional intervention. In both groups, %LBW, %LSMM, and EBEE sufficiency rate were related, and oral energy intake and PN duration were negatively related, suggesting the need for early nutritional intervention

using a nutritional pathway. Compared with the control group, the enhanced nutrition group had significantly improved nutritional indices of energy intake, EBEE sufficiency rate, and oral energy intake over time. These results support our hypothesis that by introducing new nutritional education using the HSCT nutritional pathway for patients before the start of conditioning, energy intake administered throughout the nutritional pathway is increased and body weight loss is reduced.

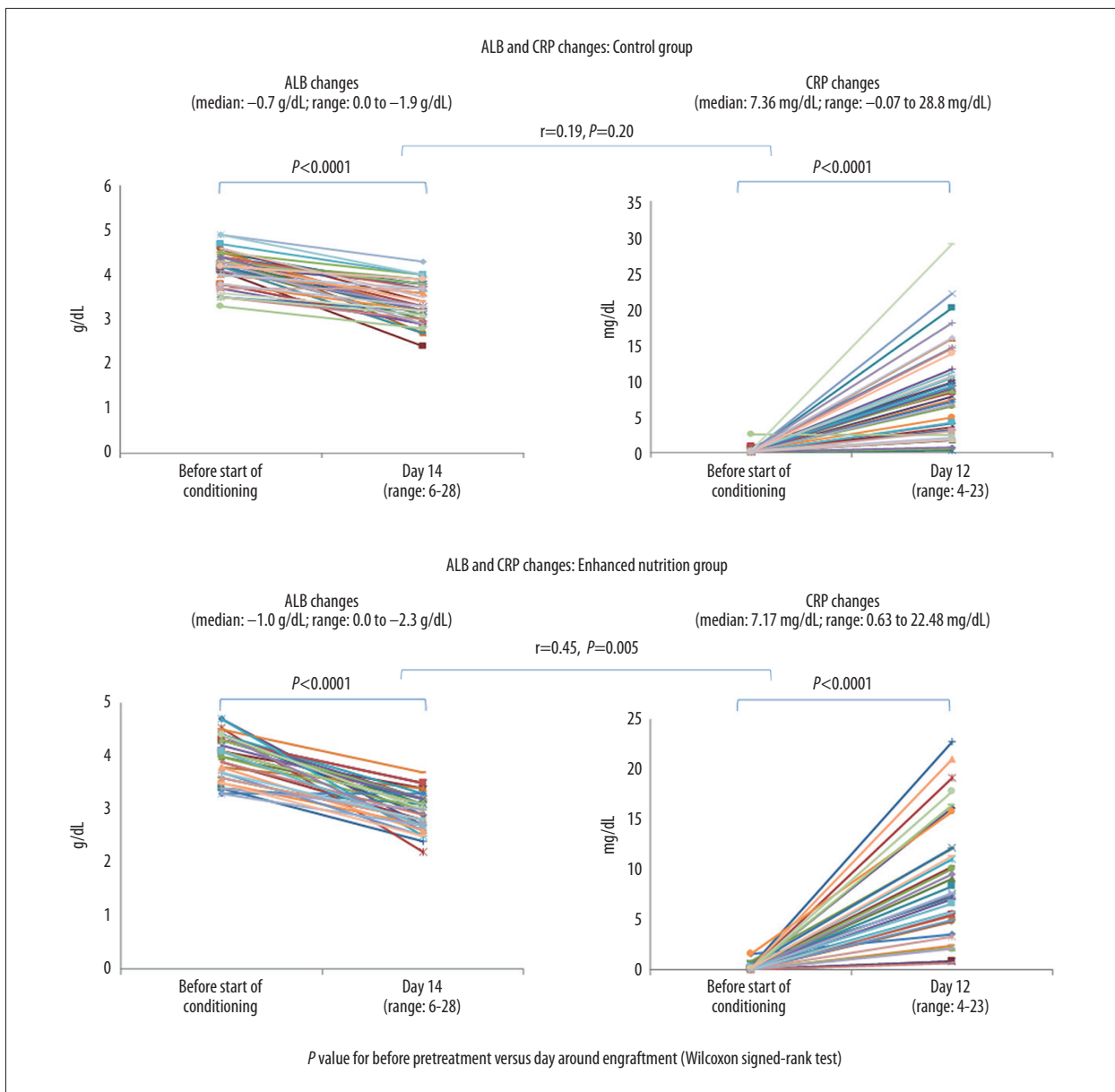
**Table 3.** EBEE rate, %LBW, and oral ingestion in gastrointestinal GvHD (grade 0 versus ≥grade 1) in each group.

Control group			P
GvHD intestinal grade	Grade 0: 29	Grade 1: 15, Grade 2: 1, Grade 3: 1	
EBEE rate/IBW% (range)	107 (73–144)	96 (74–167)	0.1716
%LBW	–3.3 (–9.8–7.4)	–9.0 (–16.7–0)	0.0006
Oral calorie intake	13 (5–28)	8 (4–14)	0.0003
Enhanced nutrition group			P
GvHD intestinal grade	Grade 0: 26	Grade 1: 9, Grade 2: 1, Grade 3: 0	
EBEE rate/IBW% (range)	112 (79–175)	116 (96–159)	0.4744
%LBW	–1.7 (–10.5–4.6)	–1.7 (–9.5–2.4)	0.9803
Oral calorie intake	13 (5–29)	13 (10–18)	0.6633

EBEE – estimated basal energy expenditure; GvHD – graft versus host disease; IBW – ideal body weight; LBW – loss of body weight. P value is before versus after assessment period (Mann-Whitney test).



**Figure 4.** (A, B) Severity score of nutrition-related adverse events and performance status (PS) over time in both groups.



**Figure 5.** Changes in C-reactive protein (CRP) and albumin (Alb) levels before the start of conditioning and around engraftment.

Given that no difference was found between the 2 groups in the amount of PN administered during the assessment period, the improvement in percentage of oral energy intake in the EBEE after PN completion and the significantly shorter PN duration in the enhanced nutrition group implies that the enhanced nutritional pathway may potentially reduce the use of medical resources. Furthermore, given the positive relationship noted between nutrition-related adverse event severity score and PS over time in both groups, we believe a reduction in PS led to a decrease in total energy expenditure (TEE) [35]. Also, it seems that nutrition-related adverse event severity score led to decreased oral intake and reduced the diet-induced energy production [36]. These results, as well as the fact that the

EBEE sufficiency rate (control group: 104%, enhanced nutrition group: 115%) was related to %LBW, are consistent with previous studies [37].

No difference in GvHD incidence was found between the control group and the enhanced nutrition group, but skin GvHD grade was significantly different between groups. The chief complaint in skin GvHD is rash, and although GvHD depends on the donor, GvHD prophylaxis, infections, and so on may have been related [22]. Resting energy expenditure was not measured in the present study, so this relationship remains unclear. Compared with the control group, the enhanced nutrition group had a higher oral energy intake but no difference



**Table 4.** Nutritional status of MAC and RIC in each group.

Control group	MAC (n: 33)	RIC (n: 13)	P
Age, mean (range)	45 (17–68)	60 (26–65)	<0.001
Preoperative BMI (range)	21.4 kg/m <sup>2</sup> (18.7–24.7)	21.1 kg/m <sup>2</sup> (18.5–24.6)	0.6455
%LBW (range)	–4.8 (–12.3–7.4)	–6.3 (–16.7–2.9)	0.3486
%LSMM (range)	–5.5 (–17.2–38.0)	–8.6 (–27.0–2.6)	0.3094
EBEE rate/IBW% (range)	105% (74–167)	103% (34–131)	0.8046
Daily oral energy intake EBEE sufficiency rate at T2 (range)	94% (30–140)	102% (34–131)	0.8434
Enhanced nutrition group	MAC (n: 27)	RIC (n: 9)	P
Age, mean (range)	56 (27–70)	63 46–69)	0.0263
Preoperative BMI (range)	21.2 kg/m <sup>2</sup> (19.1–24.6)	21.6 kg/m <sup>2</sup> (19.5–24.5)	0.9079
%LBW (range)	–0.9 (–12.3–7.4)	–3.4 (–10.5–1.0)	0.4957
%LSMM (range)	–2.0 (–16.0–12.6)	–4.1 (–20.2–3.5)	0.1919
EBEE rate/IBW% (range)	112% (79–166)	132% (91–175)	0.1923
Daily oral energy intake EBEE sufficiency rate at T2 (range)	106% (70–159)	102% (55–183)	0.6061

MAC – myeloablative conditioning; RIC – reduced-intensity conditioning; BMI – body mass index; LBW – loss of body weight; LSMM – loss skeletal muscle mass; IBW – ideal body weight; EBEE – estimated basal energy expenditure. The *P* value before versus after assessment period (Mann-Whitney test).

in gastrointestinal GvHD grade, whereas %LBW, which was related to EBEE sufficiency rate, was improved. One reason may be that even in grade 1 GvHD, in which the amount of diarrhea – the chief complaint in gastrointestinal GvHD – exceeded 500 mL/day averaged over 3 days, the nutritionist supported oral intake by providing a low-residue (low fat, low fiber) diet, thereby increasing oral nutritional intake without stressing the gastrointestinal tract.

The diet before the start of conditioning in patients undergoing HSCT is a normal diet (solid food). In our nutritional pathway (Supplementary Figures 1, 3), as shown in Figures 2 and 4, after passing through the overlapping nutrition-related adverse event severity score and initiating oral intake in patients whose appetite has recovered, the chief complaints (e.g., nausea and poor appetite) were managed by providing gelatin (which does not expand the upper gastrointestinal tract) or sorbet, ice cubes, and hot soup (which have an oral phase). The nutritional pathway is characterized by accounting for the meal completion percentage and meal preferences as the nutrition-related adverse event severity score decreases, and then, with the patient's consent, transitioning the diet to a regular diet (solid food) with meals adjusted to ensure adequate energy intake [3,4,26].

We do not use enhanced nutrition in the nutritional pathway at our facility for the following reasons: enhanced nutrition has a high osmolality and thus possibly induces diarrhea, which may confound the diagnosis of gastrointestinal GvHD [38,39]. Enhanced nutrition has also been suggested to carry a risk of saliva aspiration in the perioperative period [40]. Additionally, after the introduction of enhanced nutrition, a transition period to a regular diet is needed, and this may potentially prolong the hospital course [41–43]. In addition, we did not use glutamine, which is useful in mucosal repair, in this study, because its use was not appropriate, it does not lead to early engraftment, and evidence of its utility in gastrointestinal GvHD in human studies is lacking [44].

The nutritionist can respond to patient preference and nutrition-related adverse event severity score using various means. With enhanced oral intake, oral energy intake was improved, suggesting the possibility of maintaining quality of life [3,4,26].

We detected no differences in impact on the nutritional status of the MAC compared to the RIC [21,34]. The nutritional pathway can correspond to nutritional status MAC and RIC conditioning regimens similarly. The effectiveness of these preparative treatments can be evaluated objectively by establishing a nutritional pathway with nutritional intervention that

continuously achieves the primary endpoint of prevention of loss of body weight [26].

Our study design did not allow for a comparable incidence of GvHD between the 2 groups, which would necessitate randomizing the 2 groups while keeping the human leukocyte antigen allele consistent. In fact, such manipulation of GvHD incidence and pre-transplantation risk intervention are not applicable to the practical clinical use of the nutritional pathway and was neither practical nor explicable to patients [45]. As such, a limitation of this study was that the effect of immunosuppressive agents and steroids on GvHD was not evaluated [46]. In addition, our study did not include data on infections during the HCT period and any viral or fungal stomatitis [47].

In the present study, we considered nutrition-related adverse events (severity score) and gastrointestinal GvHD in patients

undergoing HSCT using the nutritional pathway and used the EBEE sufficiency rate to monitor nutritional intake and factors associated with body composition. Our results suggest that initiation of nutritional intervention to improve prevention of high %LBW to <7.5% over 3 months was necessary. The results of this study are important and may help to improve the quality of nutritional care for bone marrow transplant patients.

### Conclusions

In conclusion, our nutritional pathway for patients undergoing HSCT includes nutritional education before the start of conditioning and provides nutritional support that takes gastrointestinal GvHD and nutrition-related adverse events into account. This nutritional pathway was shown to enhance oral intake and may help reduce weight loss.

### Supplementary Data

Hospitalization (nutritional) treatment plan (for patients undergoing hematopoietic stem cell transplantation)

Attending nutritionist: @USERNAME

(@patient\_ID) @patient\_full name

	The day before the start of conditioning (T1: baseline)	Transplant pretreatment Transplant method	Transplantation day (Day 0)	Early post-transplant period	Middle post-transplant period	The day after PN completion (T2)	Day 100	Late post-transplant period
Date	/		/		/		/	
Nutrition plan	You cannot drink tap water Your food will be covered with plastic wrap 1. Your nutritionist will confirm with the manufacturer that your drinking water has been sterilized by boiling. 2. We will ask your food preferences. 3. We will explain the changes in diet based on your symptoms during the hospital stay. 4. Please write down how much you ate on the diet form. (Example: Ate everything: 10, ate half: 5, did not eat: 0. <b>Half diet, low fiber, low fat [immune diet]</b> 5 Porridge 100 g 3 Boiled Chinese vegetables 0 Sesame tofu 5 Boiled sweet potatoes 10 Tea Name: Mishima Taro Ward: 9019 West Sunday, January 10, Lunch You will find a menu form on top of your meal. Please write the amount you ate for each meal, and leave form in the folder. Your nutritionist will ask you about diet during treatment, adjust the meal, collect the menu form, and calculate your nutritional intake.		Nutritionist visits patient's room, adjust diet within immunocompromised diet based on patient symptoms and preference, and reports to physician Normal immune diet If poor oral intake, high-calorie intravenous nutrition will be started Individualized response: cold noodle or porridge (adjustable amount, canned fruit, gelatin, sherbet, tofu, etc. Light I: 1. Two fruits (repeated during the course of the day) 2. Soup, gelatin, juice, etc. 3. Salad, vinegary salad, etc. There are choices within the above 3 items Light II: 1. Entree consists of a small amount of potato porridge or sandwich 2. Salad or seasoned dish, shumai dumplings. Small amount of baked salmon, etc. 3. Sweet item such as fruit or gelatin. There are choices within the above 3 items. Half diet: 1-3 food item choices. Lunch includes a half-portion of tasty entrees such as sushi or omelet rice. The portion size is halved, making it easy to eat even with a poor appetite.		Normal immune diet Prohibit food item orders will be confirmed by the physicians Patients will be asked to record meals during out-of-hospital stays as necessary. Instructions on diet after hospital discharge will be given as necessary.			
Intervention by nutritionist	The nutritionist will measure body composition. Nutritional intake amount will be calculated from the patient-completed diet form (meal intake amount)		1. The nutritionist visits the patient's room daily, delivers the best proposal based on meal completion proportion (amount consumed) and patient preference. 2. The nutrition amount, oral intake, and parenteral nutrition will be calculated. (Food brought in will be calculated upon confirmation by the physician). 3. The desired menu will be randomly chosen from multiple food and proposed to the patient. 4. Specific request will be prepared and provided if ingredients can be obtained		After completion of parenteral nutrition, the nutritionist will measure body composition.			
Communication	<b>Body composition measurements</b> 1. Patient with pacemakers cannot undergo these measurements 2. Please use the restroom before measurements 3. Please lay flat, facing upwards for at least 5 minutes before measurement. The measurement take about 2 minutes. 4. You may not exercise, take a bath, or eat for 2 hours before the measurement.							
Precautions								

**Supplementary Figure 1.** Nutritional pathway for patients undergoing hematopoietic stem cell transplantation: Every day a nutritionist visits the patient at the bedside from before the start of conditioning to completion of parenteral nutrition (PN) and inquires about the patient's preferences and adverse events, reports to the physician the energy and protein intakes from both PN and oral nutrition, confirms the physician's orders for dietary adjustment, and applies dietary changes in real time.

Prohibited food items in immune diet	Precautions
Fresh vegetables	Can disinfect using strongly acidic water (50 ppm)
Fruits eaten fresh with skin (strawberries, etc.)	May eat jam and jello (food made for a person for one meal)
Homemade pickles, pickled plum, natto (fermented soy beans), chesee	Prohibited. May eat processed chesee
Raw miso, cream, honey, tofu, dried fruits, nuts, meat, fish, egg, dairy	May eat after heating (must be heated for over 1 min with central temperature 85°C)
Grapefruit or juice, etc. (during immunosuppressive treatment)	Prohibited
Tap water, unheated drinking water (ice)	Prohibited. Heated drinking water: small container; must be consumed same day
Food prepared more than 2 hours before	Prohibited
Dessert (ice cream, etc.), snacks	May eat if individually wrapped and heat processed. Dried shredded aquad prohibited
Unwrapped food	Prohibited. May eat food wrapped immediately after preparation

**Supplementary Figure 2.** The food hygiene protocol for Hematopoietic Stem Cell Transplant in the Dietary Department Shizuoka Cancer Center.

Nutrition intervention method with nutritional pathway for HSCT according to the Aoyama formula [19,20]

Adverse events: symptoms of CTCAE	First step	Examples
Anorexia, fever	Lightly sweetened foods, cooled foods	2 kinds of fruits, sherbet (fruit flavor), vegetable juice, etc.
Vomiting, nausea	Room-temperature and semi-solid foods	Watery gelatin, crushed gelatin, ice cream with a long melting time, etc. (Liquid food not diffusing in upper digestive tract will do)
Mucositis/stomatitis	Softened and bland foods	Steamed egg hotchpotch, tofu, warm soup, etc.
Taste disorder	Simple-tasting foods or bland foods, odorless foods (cold foods) Absent sense of smell; Patient's favorite foods	2 kinds of gelatin (for distinguishing the taste of fruit from water), cold milk, fruit juice, water ice cubes, traditional Japanese food (e.g. miso soup, salty rice crackers), etc. For absent sense of smell and dry mouth, oral spray for dry mouth will help. (Patient can also try the following: chewing gum, carbonated beverage, tongue brush, etc.) [19]
Diarrhea	Low-fat and low-fiber diet, warm bland foods	Traditional Japanese food (e.g. warm noodle stew, rice gruel). Enteral nutrition should be restricted for high osmolality (>280 mOsm/L) [20]

CTCAE: Common Terminology Criteria for Adverse Events

**Supplementary Figure 3.** The nutritional interventions protocol for Hematopoietic Stem Cell Transplant of Shizuoka Cancer Center: Aoyama formula.

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