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Effect of Early Nutritional Support on Quality of Life by EORTC QLQ-C30 in Allogeneic Hematopoietic Stem Cell Transplantation

Ayaka Inden[1,2], Takayoshi Tsukahara[1], Eiko Tachibana[1], Yasuyuki Nagata[3], Takaaki Ono[4], Akihiko Kato[2]

[1]Graduate School of Nutritional Sciences, Nagoya University of Arts and Sciences, Aichi, Japan, [2]Clinical Nutrition Unit, Hamamatsu University Hospital, Shizuoka, Japan, [3]Division of Hematology, Hamamatsu University School of Medicine, Shizuoka, Japan, [4]Department of Transfusion and Cell Therapy, Hamamatsu University School of Medicine, Shizuoka, Japan

Abstract

Purpose: Increasing attention is being paid to the importance of nutritional management of allogeneic hematopoietic stem cell transplant (allo-HSCT) patients. However, few studies have conducted detailed evaluations of both nutritional intake and quality of life (QOL) in allo-HSCT patients. Therefore, we investigated the nutritional status and quality of life of our allo-HSCT patients.

Methods: The subjects were 26 adults who underwent allo-HSCT at Hamamatsu University Hospital between August 2018 and October 2021. Early nutritional intervention was provided from the time of the decision to perform allo-HSCT to the time of discharge, and it incorporated regular QOL assessments. The analyzed indices were nutritional intake, anthropometric measurements, body mass index (BMI), grip strength, body composition analyzer (InBody S10) measurements, and blood laboratory values including transthyretin levels. QOL was assessed using the QLQ-C30 questionnaire of the European Organization for Research and Treatment of Cancer (EORTC) (version 3.0) and calculated according to the EORTC scoring manual. The indices were compared at pre-transplantation, 30 days post-transplantation, 60 days post-transplantation, and at discharge. The association between pre-transplantation nutritional status and QOL was examined.

Results: The median hospital stay after transplantation was 97 days (range, 78-123 days). Energy intake was maintained at 31 kcal/day/kg through 30 days post-transplantation, 60 days post-transplantation, and discharge, and protein intake was maintained at 1.0 g/day/kg throughout all time periods. There was a significant positive correlation between the pre-transplantation transthyretin level and the 60-day post-transplantation QOL scores for "global health", "physical functioning", "cognitive functioning", and "emotional functioning", and there were significant negative correlations with "fatigue" and "pain" that indicated improvement.

Conclusion: Early nutritional management of allo-HSCT patients prior to transplantation allowed maintenance of nutritional intake, and higher pre-transplant transthyretin levels were associated with higher QOL scores at 60 days post-transplantation.

Key words allogeneic hematopoietic stem cell transplant, nutrition, quality of life, Nutrition Support Team

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Correspondence: Ayaka Inden, Clinical Nutrition Unit, Hamamatsu University Hospital, 1-20-1 Handayama, Higashi-ku, Hamamatsu city, Shizuoka 431-3192, Japan, E-mail: ayaka15@hama-med.ac.jp

1. Introduction

The number of hematopoietic stem cell transplantations (HSCTs) performed in Japan has increased dramatically since 1990, and more than 5,000 HSCT procedures are now performed annually. The collection and analysis of data regarding complications and the course after HSCT have played an important role in improving HSCT outcomes worldwide[1].

Allogeneic hematopoietic stem cell transplantation (allo-HSCT), a conditioning regimen with high-dose chemotherapy and whole-body radiation prior to transplantation, causes oral mucositis, diarrhea, nausea and vomiting, taste abnormalities, and commonly, loss of

appetite. In addition, graft-versus-host disease (GVHD) and various complications may occur following transplantation. These post-transplant symptoms reduce oral intake and can in turn impair nutritional status and quality of life (QOL).

Patients with hematopoietic tumors have been shown to have lower QOL and health-related QOL (HRQOL) compared with the general population. Therefore, it is important to assess QOL at the beginning of treatment[2]. Allo-HSCT also has short- and long-term effects on QOL and physical and psychological health. Many patients experience significant mental distress after HSCT, and the treatment has a negative influence on QOL and systemic function[3-8]. In the basic guidelines for allo-HSCT at Hamamatsu University Hospital (hereafter "our hospital"), the patient remains in a clean room from pre-transplantation to discharge, and therefore receives treatment in a closed environment. This setting leads to a decrease in physical activity compared with patients admitted to a general hospital room.

Adverse physical symptoms are a general indicator of the physical domain of HRQOL[9]. It has been suggested that HSCT is associated with decreased psychological domains of HRQOL[10], increased distress, anxiety, and depression[11-15], and decreased health outcomes and survival[16,17]. Numerous studies have focused on the physical function of patients post-HSCT. A certain percentage of patients still suffer from long-term side effects such as chronic GVHD and do not reach pre-transplantation HRQOL levels at 2 years post-transplantation[18]. Others have reported that full recovery is a three- to five-year process[8]. We previously reported that nutritional management is necessary from the early stage, because nutritional status will deteriorate after transplantation even with Nutrition Support Team (NST) intervention[19]. As a result of this finding, we have implemented aggressive early (pre-transplantation) nutritional intervention as a new NST protocol. Patients who received this intervention had better QOL than those described in other reports[20]. However, few studies have focused on changes in QOL and nutritional care during hospitalization. Therefore, we analyzed the trends in nutritional status and QOL of allo-HSCT patients over time at our hospital. We hypothesized that a nutritional intervention protocol would improve the nutritional status and QOL of patients who had undergone allo-HSCT.

2. Patients and Methods

Patients

Of 30 adults who underwent allo-HSCT at our hospital between August 2018 and October 2021, 26 were enrolled in the study. Four patients who died during the observation period were excluded.

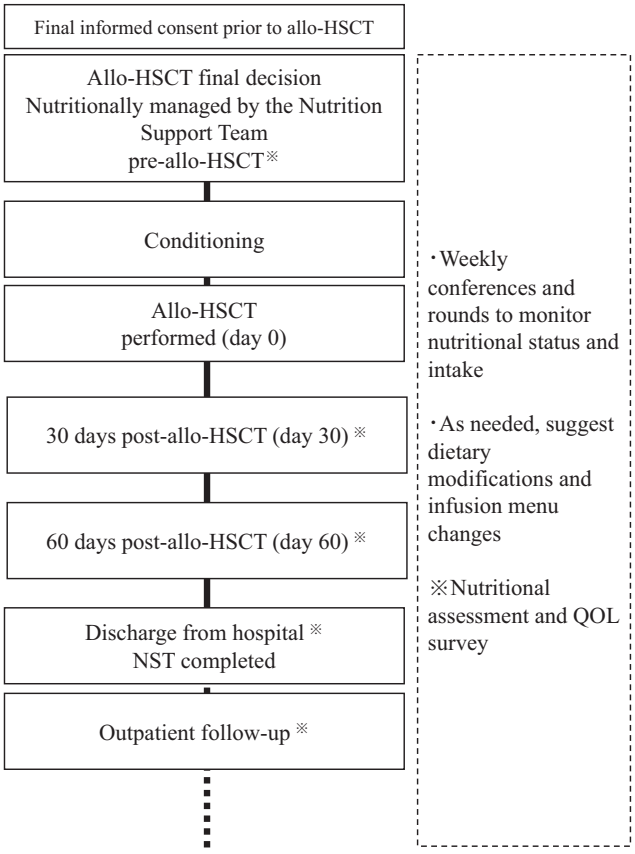

Figure 1. Nutritional management protocol for allo-HSCT patients in our hospital
allo-HSCT, allogeneic hematopoietic stem cell transplantation; NST, nutrition support team; QOL, quality of life

Nutritional management of patients with allo-HSCT

Figure 1 shows the nutritional management protocol implemented at our hospital for allo-HSCT patients. After obtaining the patient's final informed consent before allo-HSCT, NST intervention was initiated as soon as the transplant decision was made, and weekly conferences and rounds were held to monitor nutritional status and intake. As needed, we also suggested dietary modifications and considered changes and additions to the content of nutritional supplements and changes to the parenteral nutrition menu. The intervention was terminated at the time of discharge, after which the patient was followed up at an outpatient clinic. Detailed nutritional assessments were performed at pre-transplantation (pre-conditioning regimen), at 30 days post-transplantation, at 60 days post-transplantation, and at discharge. In principle, oral intake was continued until the time of discharge. In cases where diet alone was insufficient, nutritional supplements were added. At the time of discharge, dietary intake was by oral intake alone in all patients.

Nutritional assessment index

The survey items included nutritional intake, body measurements (triceps skinfold [TSF] and arm muscle circumference [AMC]), body mass index (BMI), grip strength, body composition analyzer measurements (InBody S10, InBody Japan Inc., Tokyo, Japan; skeletal muscle mass index (SMI), extracellular water/total body water [ECW/TBW] and phase angle [PA]), and blood test values (total protein, albumin, transthyretin, cholinesterase, triglycerides, total cholesterol, zinc, C-reactive protein, white blood cell count, hemoglobin, platelet count, and total lymphocyte count). Since evaluations were performed every 30 days, it was necessary to assess nutritional status using a rapid turnover protein that has a short blood half-life. Therefore, transthyretin, which has a half-life of 1.9 days, was used to evaluate the association between nutritional status and QOL.

QOL score

We used the QOL questionnaire of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30[21] (version 3.0). Specifically, the Japanese version of the EORTC QLQ-C30, which has been shown to be reliable and valid[22], was used in the present study. Prior permission to use this questionnaire was obtained from EORTC and the developer of the Japanese version, Kojiro Shimozuma. The participants were asked to answer a total of 30 self-administered questions about their global health; five functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning); and nine symptom scales (nausea and vomiting, fatigue, dyspnea, pain, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). QOL scoring followed the EORTC scoring manual[23]. Higher standardized scores on the global health and functional scales indicated better status, whereas lower standardized scores on the symptom scale indicated better status.

Ethical considerations

Approval to conduct this study was obtained from the Ethics Committee of Hamamatsu University School of Medicine (Approval No. 18-077). Consent was obtained on an opt-out basis.

Statistical analyses

The following assessments of nutritional indices and QOL scores were performed. The Friedman test (post hoc test: Bonferroni method) was used to compare the results at pre-transplantation, 30 days post-transplantation, and 60 days post-transplantation. Spearman's rank correlation coefficient was used to evaluate the association between the pre-transplantation transthyretin level and the QOL score at 60 days post-transplantation, with a significance level of less than 5%. EZR[24] version 1.54 was used as the statistical software.

3. Results

Patient characteristics

The median age of the 26 patients was 46 years (range, 33-50 years; male, 38.0% and female, 62.0%). The underlying diseases were acute myeloid leukemia (35.0%), chronic myeloid leukemia (15.0%), T-cell acute lymphocytic leukemia (11.0%), myelodysplastic syndrome (11.0%), acute lymphoblastic leukemia (8.0%), B lymphoblastic leukemia (8.0%), Hodgkin's lymphoma (8.0%), and adult T-cell leukemia (4.0%). The types of allo-HSCT were cord blood transplantation (70.0%), bone marrow transplantation (15.0%), and peripheral blood stem cell transplantation (15.0%). The type of conditioning regimen was myeloablative conditioning (92.0%) and reduced intensity conditioning (8.0%). Total body irradiation was standard dose in 70.0% and not standard dose in 30.0%. Grade II-IV acute GVHD was seen in 38.0% of all patients. No post-transplantation complications occurred, but post-transplantation infections occurred in 27.0%. There was human leukocyte antigen mismatch in 73.0%. The donor was unrelated in 89.0%. The median hospital stay after transplantation was 97 days (range, 78-123 days) (**Table 1**).

Comparison of nutritional indices and QOL scores

Nutritional assessment index

Energy intake was maintained at 31 kcal/day/kg through the 30 days post-transplantation, 60 days post-transplantation, and at discharge. Protein intake was maintained at 1.0 g/day/kg throughout all periods. There was no difference in energy or protein intake by time point.

Regarding the physical measurements, there was a significant decrease in %TSF at 60 days post-transplantation and at discharge (P=0.002) and a significant decrease in %AMC at discharge (P=0.007) compared with pre-transplantation. BMI decreased significantly between 30 and 60 days post-transplantation and at discharge (P<0.001). Grip strength decreased between pre-transplantation and 60 days post-transplantation and at discharge for both men (P=0.001) and women (P=0.012).

SMI calculated by the body composition analyzer decreased significantly between 30 days post-transplant and discharge for both men (P=0.001) and women (P=0.007), whereas ECW/TBW and PA increased signifi-

Table 1. Patients' characteristics (*n*=26)

Age, y		%
Median (interquartile range)	46 (33–50)	
Sex, n		
Men	10	38.0%
Women	16	62.0%
Diagnosis, n		
Acute myelogenous leukemia	9	35.0%
Chronic myelogenous leukemia	4	15.0%
T-cell lymphoblastic leukaemia	3	11.0%
Myelodysplastic syndromes	3	11.0%
Acute lymphoblastic leukemia	2	8.0%
B lymphoblastic leukemia	2	8.0%
Hodgkin's lymphoma	2	8.0%
Adult T-cell leukemia	1	4.0%
Conditioning regimen, n		
Myeloablative conditioning	24	92.0%
Reduced intensity conditioning	2	8.0%
Nonmyeloablative conditioning	0	0.0%
Standard-dose total body irradiation, n		
No	8	30.0%
Yes	18	70.0%
Transplantation, n		
Cord blood transplantation	18	70.0%
Bone marrow transplantation	4	15.0%
Peripheral blood stem cell transplantation	4	15.0%
Acute GVHD, n		
No	12	47.0%
Yes (Grade I)	4	15.0%
Yes (Grade II–IV)	10	38.0%
Chronic GVHD, n		
No	25	96.0%
Yes	1	4.0%
Infection, n		
No	19	73.0%
Yes	7	27.0%
*Details (Percentage is the number of Yes)		
Cytomegalovirus	2	29.0%
Human herpesvirus 6	2	29.0%
Pulmonary mycosis	2	29.0%
Adenovirus hemorrhagic cystitis	1	13.0%
Complications, n		
No	26	100.0%
Yes	0	0.0%
HLA-mismatch, n		
No	7	27.0%
Yes	19	73.0%
Donor, n		
Unrelated	23	89.0%
Related	3	11.0%
Number of days in hospital after transplantation		
Median (interquartile range)	97 (78–123)	

GVHD, graft-versus-host disease; HLA, human leukocyte antigen

cantly at 30 days post-transplantation, 60 days post-transplantation, and at discharge (P<0.001) compared with pre-transplantation.

Serum total protein and serum albumin levels were significantly lower at 30 days post-transplant and at discharge compared to pre-transplantation (P<0.001), but they tended to recover at discharge. Transthyretin levels remained within the reference range. Zinc levels were significantly lower at 30 days and 60 days post-transplantation (P=0.006). White blood cell counts were significantly higher at 60 days post-transplant and at discharge compared to pre-transplantation (P<0.001). Hemoglobin levels, platelet levels, and total lymphocyte counts all increased significantly between 30 days post-transplantation and discharge (P<0.001) (**Table 2**).

QOL Score

"Global health" was significantly decreased at 30 days post-transplantation compared to pre-transplantation, but it improved significantly from 30 to 60 days post-transplantation and from 30 days post-transplantation to discharge (P<0.001). On the functional scale, "physical functioning" scores decreased significantly at 30 and 60 days post-transplantation compared to pre-transplantation, but they improved significantly from 30 days post-transplantation to discharge (P<0.001). The score for "role functioning" decreased significantly at 30 days post-transplantation (P=0.004). On the symptom scale, scores for "nausea and vomiting," "fatigue," "appetite loss," and "diarrhea" were significantly worse at 30 and 60 days post-transplantation compared to pre-transplantation, but they improved significantly from 30 days and 60 days post-transplantation to discharge (P<0.001). Scores for "pain" and "insomnia" were significantly worse at 30 days post-transplantation compared to pre-transplantation, but they improved significantly from 30 days post-transplantation to discharge (P<0.001) (**Table 3**).

Associations of the pre-transplant transthyretin level with the QOL scores at 60 days post-allo-HSCT

There were significant positive correlations between the pre-transplantation transthyretin level and the 60 days post-transplant QOL scores for "global health" (r=0.459, P=0.027) and the functional scales of "physical functioning" (r=0.512, P=0.012), "cognitive functioning" (r=0.448, P=0.032), and "emotional functioning" (r=0.551, P=0.006). The symptom scales of "fatigue" (r=-0.511, P=0.012) and "pain" (r=-0.544, P=0.007) showed a significant negative correlation. These findings indicate that patients with higher levels of transthyretin pre-transplantation had improved QOL after transplantation (**Figure 2**).

Table 2. Changes in nutritional intake and nutritional assessment after allo-HSCT (*n*=26)

Nutrition index		*pre allo-HSCT*	*30 days post-allo-HSCT*	*60 days post-allo-HSCT*	*at discharge IQR 97 (78–123)*	P<0.05[1)]
Nutrient intake						
Energy, kcal/day/kg		31 (27–39)	31 (28–36)	31 (23–36)	32 (25–41)	
Protein, g/day/kg		1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	1.1 (0.7–1.4)	
Physical measurements						
TSF, mm		15.0 (12.0–16.0)	13.0 (10.0–15.8)	13.5 (10.0–15.0)	10.0 (8.3–14.5)	d
%TSF		109.1 (81.7–137.4)	100.0 (80.3–113.9)	99.3 (77.3–110.1)	81.3 (61.8–109.2)	bd
AMC, cm		21.7 (19.9–23.8)	21.9 (19.8–23.8)	21.2 (19.0–22.9)	20.9 (19.0–22.5)	de
%AMC		96.3 (94.4–108.2)	99.5 (92.4–106.1)	94.5 (89.7–103.9)	95.1 (87.4–100.9)	de
BMI, kg/m^2		20.5 (18.1–22.3)	20.5 (18.3–23.1)	20.4 (18.0–21.9)	19.5 (17.2–21.0)	cdef
Grip strength, kg	Men	34.6 (33.6–38.6)	33.2 (27.2–36.9)	31.5 (26.6–34.3)	28.8 (23.4–30.7)	bd
	Women	22.9 (18.5–24.2)	18.9 (16.9–21.8)	18.7 (17.0–21.8)	18.3 (16.5–20.3)	bd
Body Composition Analyzer						
SMI, kg/m^2	Men	7.3 (7.1–7.7)	7.4 (7.0–7.9)	6.9 (6.6–7.2)	6.6 (6.3–6.9)	e
	Women	5.6 (5.3–5.9)	5.7 (5.1–5.8)	5.4 (5.2–6.1)	5.1 (4.4–5.6)	ef
ECW/TBW		0.394 (0.387–0.402)	0.401 (0.395–0.407)	0.401 (0.387–0.402)	0.401 (0.398–0.408)	abd
PA, degrees		4.9 (4.4–5.3)	4.2 (3.7–4.6)	4.3 (3.7–4.6)	4.0 (3.6–4.3)	abd
Laboratory date						
TP, g/dL		6.6 (6.3–6.9)	5.8 (5.5–6.8)	5.9 (5.5-6.2)	6.1 (5.5-6.3)	abd
Alb, g/dL		4.2 (4.0-4.5)	3.6 (3.4–3.9)	3.6 (3.5–4.0)	3.9 (3.7–4.2)	abd
TTR, mg/dL		25.0 (22.1–30.9)	23.1 (18.6–29.0)	23.8 (20.0–26.7)	27.4 (21.6–33.4)	
ChE, U/L		302 (267–328)	285 (244–303)	240 (196–267)	225 (175–266)	abd
TG, mg/dL		168 (111–231)	146 (106–196)	169 (152–249)	202 (156–300)	cde
TC, mg/dL		191 (159–219)	147 (135–168)	155 (142–178)	179 (164–213)	e
Zn, μg/dL		74 (67–83)	89 (81–98)	84 (75–90)	81 (70–88)	ab
CRP, mg/dL		0.17 (0.04–0.28)	0.20 (0.07–0.44)	0.19 (0.08–0.32)	0.08 (0.04–0.34)	
WBC, /μL		2,720 (2,243–3,783)	3,330 (2,435–4,883)	6,000 (4,595–10,170)	5,830 (4,060–8,390)	bd
Hb, g/dL		10.5 (9.1–11.3)	8.7 (8.2–9.5)	10.0 (9.1–10.7)	10.1 (9.2–10.8)	ace
PLT, 10^4/μL		19.6 (9.0–24.9)	4.4 (2.4–8.1)	10.6 (6.1–14.5)	13.2 (6.9–15.9)	ae
TLC, /μL		710 (539–1,035)	458 (334–574)	869 (601–1,299)	1,015 (743–1,394)	ce

Data are presented as the median (interquartile range)

1) Indicates less than P<0.05 Friedman test (Post-hoc test: Bonferroni method)

a, pre-allo-HSCT vs 30 days post-allo-HSCT; b, pre-allo-HSCT vs 60 days post-allo-HSCT; c, 30 days post-allo-HSCT vs 60 days post-allo-HSCT; d, pre-allo-HSCT vs at discharge; e, 30 days post-allo-HSCT vs at discharge; f, 60 days post-allo-HSCT vs at discharge

allo-HSCT, Allogeneic Hematopoietic Stem Cell Transplantation; IQR, interquartile range; TSF, triceps skinfold; AMC, arm muscle circumference; BMI, body mass index; SMI, skeletal muscle mass index; ECW/TBW, extracellular water/total body water; PA, phase angle; TP, total protein; Alb, albumin; TTR, transthyretin; ChE, cholinesterase; TG, triglycerides; TC, total cholesterol; Zn, zinc; CRP, C-reactive protein; WBC, white blood cell count; Hb, hemoglobin; PLT, platelet count; TLC, total lymphocyte count

4. Discussion

This study investigated trends in nutritional status and QOL in allo-HSCT patients before and after transplantation. The results showed that energy and protein intakes were generally maintained at 31 kcal/day/kg and 1.0 g/day/kg, respectively, through pre-transplantation, 30 days post-transplantation, 60 days post-transplantation, and at discharge. In addition, there were associations between the pre-transplantation transthyretin level and QOL scores at 60 days post-transplantation for "global health", functional scales ("physical functioning", "cognitive functioning", and "emotional functioning"), and symptom scales ("fatigue" and "pain").

According to the Japanese parenteral and enteral nutrition guidelines[25], nutritional management in HSCT is absolutely necessary because all patients undergoing HSCT are at nutritional risk. It is recommended that nutritional therapy should be started early, even if there are no nutritional disorders before treatment begins. The American Society for Parenteral and Enteral Nutrition guidelines[26] also state that all patients undergoing HSCT are considered to be at nutritional risk and recommend that they undergo nutritional screening to develop a nutrition care plan and identify patients who require nutritional assessment. Furthermore, the European Society for Clinical Nutrition and Metabolism guidelines[27] on

Table 3. Changes in QLQ-C30 score after allo-HSCT (*n*=26)

QLQ-C30 scale	*pre allo-HSCT*	*30 days post-allo-HSCT*	*60 days post-allo-HSCT*	*at discharge IQR 97 (78–123)*	P<0.05[1)]
global health	71 (50–83)	38 (27–50)	50 (38–58)	67 (50–67)	ace
Functional scale					
physical functioning	87 (80–92)	67 (42–78)	67 (53–84)	80 (69–87)	abe
role functioning	83 (67–100)	59 (33–79)	67 (33–100)	83 (67–100)	a
cognitive functioning	100 (83–100)	75 (67–83)	67 (67–100)	83 (71–100)	
emotional functioning	83 (67–92)	75 (60–90)	75 (67–92)	83 (75–92)	e
social functioning	67 (37–83)	67 (33–83)	67 (33–92)	67 (37–96)	
Symptom scale					
nausea and vomiting	0 (0–0)	50 (33–67)	33 (25–67)	0 (0–33)	abef
fatigue	33 (14–41)	56 (36–86)	44 (33–67)	33 (22–53)	abef
dyspnea	0 (0–33)	33 (0–61)	33 (17–33)	33 (0–33)	
pain	0 (0–29)	33 (17–50)	33 (0–50)	0 (0–17)	abe
insomnia	17 (0–33)	67 (33–92)	33 (33–67)	33 (0–33)	ae
appetite loss	0 (0–33)	84 (42–100)	67 (33–100)	33 (0–67)	abef
constipation	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
diarrhea	0 (0–33)	33 (33–67)	33 (17–50)	0 (0–33)	abef
financial difficulties	33 (0–67)	33 (0–67)	33 (0–67)	33 (0–59)	

Data are presented as the median (interquartile range)

1) Indicates less than P<0.05 Friedman test (Post-hoc test: Bonferroni method)

a, pre-allo-HSCT vs 30 days post-allo-HSCT; b, pre-allo-HSCT vs 60 days post-allo-HSCT;
c, 30 days post-allo-HSCT vs 60 days post-allo-HSCT; d, pre-allo-HSCT vs at discharge;
e, 30 days post-allo-HSCT vs at discharge; f, 60 days post-allo-HSCT vs at discharge

Global health and functional scales: Higher standardized scores indicate better health and function.

Symptoms scales: Lower standardized scores indicate improvement in symptoms.

allo-HSCT, Allogeneic Hematopoietic Stem Cell Transplantation; IQR, interquartile range

nutrition for cancer patients recommend maintaining physical activity and ensuring adequate nutritional intake during pre-transplantation high-dose chemotherapy and post-HSCT. Therefore, nutritional management at pre-transplantation is important. Allo-HSCT involves a conditioning regimen with a combination of higher-dose and more intense chemotherapy and whole-body radiation than is commonly used. The risk of malnutrition after transplantation is high because adequate oral intake cannot be maintained due to the development of oral mucositis, nausea, vomiting, and diarrhea[28]. Reports on diet and its impact on post-HSCT complications are scarce; moreover, the focus has been primarily on nutrition immediately after transplantation[29]. In contrast, our NST provided early nutritional intervention to improve pre-transplantation nutritional status.

In this study, QOL was evaluated along with nutritional status. HRQOL assesses physical, psychological, social, and emotional functioning from the patients' experience and perspective, and it can identify individuals who may benefit from clinical interventions. An association has been shown between nutritional status and HRQOL outcomes in other cancer types, with malnourished patients reporting lower QOL than well-nourished patients[30]. The QOL scores of patients in our hospital were higher than those of patients before treatment for other cancers that were reported in a previous study[20]. QOL is an important metric that reflects the health status of cancer patients, and it is significantly impacted by nutritional factors[31]. However, there are no reports of the association of nutritional status and QOL in HSCT. In particular, QOL after allo-HSCT may be affected by acute and chronic GVHD, infections, and complications. In the present study, there was no bias in post-transplant QOL scores based on the presence or absence of acute GVHD or infection, but further study is needed to examine more cases. In addition, complications and chronic GVHD are factors that are inherently affected, and it is necessary to look at associations with these factors.

Although the data are not shown, QOL at 30 days was lower at post-transplantation than pre-transplantation, but recovered at discharge, and there was no correlation between pre-transplantation transthyretin levels and QOL at either 30 days post-transplantation or at discharge, because there was little difference in the level in most patients. Therefore, we investigated the relationship between pre-transplantation transthyretin levels and QOL at 60 days post-transplantation, where the distribution of the level varied. There were significant positive correlations between pre-transplantation transthyretin levels and the 60-day

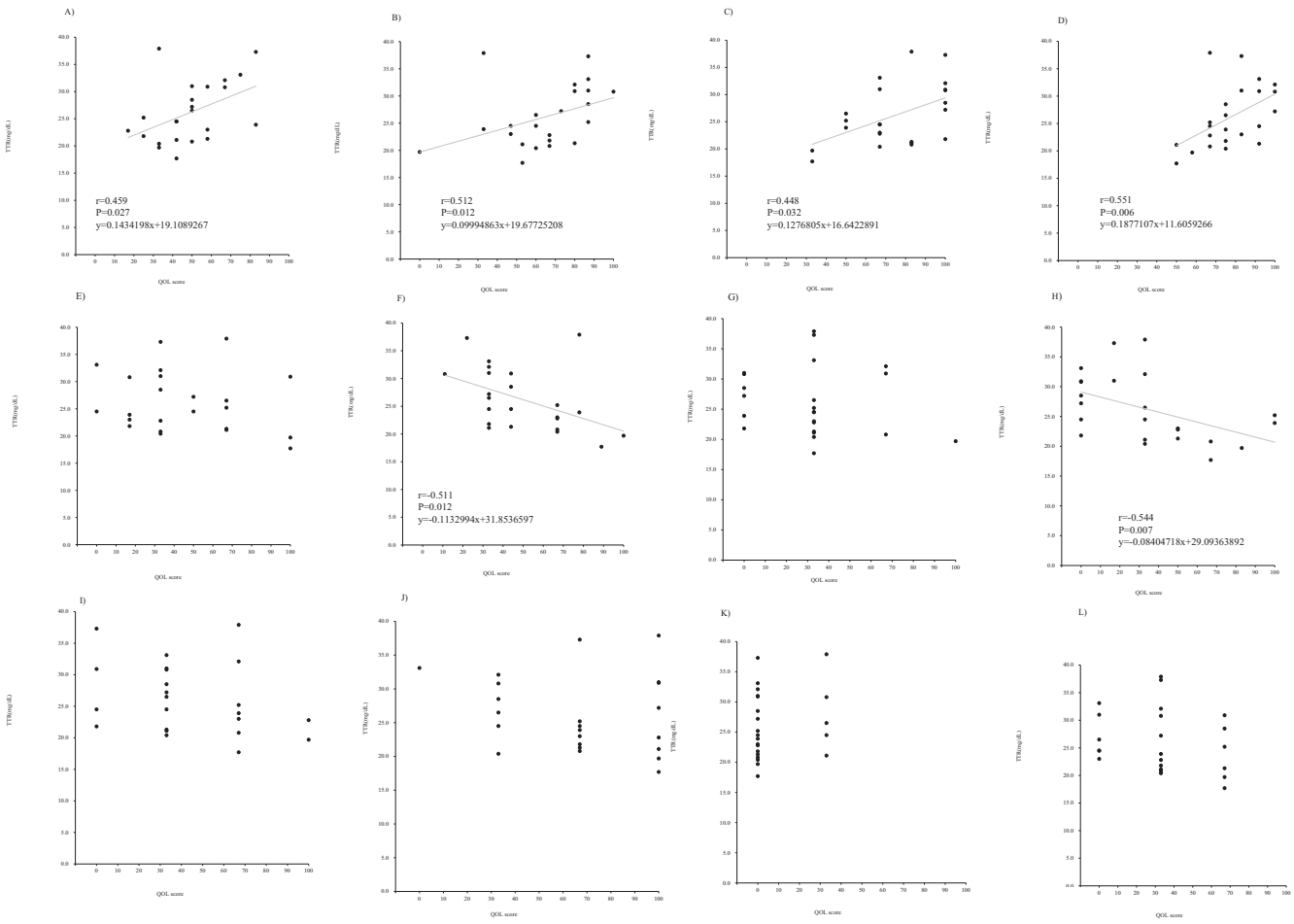

Figure 2. Association of the pre-allo-HCST transthyretin level with the QOL score at 60 days post-allo-HSCT
Data are shown for (A) global health; the functional scales of (B) physical functioning, (C) cognitive functioning, (D) emotional functioning; and the symptom scales of (E) nausea and vomiting, (F) fatigue, (G) dyspnea, (H) pain, (I) insomnia, (J) appetite loss, (K) constipation, and (L) diarrhea.
For global health and the functional scales (B, C, D), higher standardized scores indicate better health and function. For the symptom scales (E, F, G, H, I, J, K, L), lower standardized scores indicate improvement in symptoms.
allo-HSCT, allogeneic hematopoietic stem cell transplantation; TTR, transthyretin

post-transplantation QOL scores for "global health" and functional scales of "physical functioning", "cognitive functioning," and "emotional functioning", and significant negative correlations for the symptom scales of "fatigue" and "pain". These findings indicate that nutritional management during both transplantation and early pre-transplantation is important and is associated with recovery of QOL after transplantation. Continued undernutrition leads to progressive muscle loss and muscle weakness that result in reduced strength and physical function, leading to reduced activity, reduced appetite, and further undernutrition. Nutritional status and physical function are linked, and the level of activities of daily living is also a component in assessing QOL. Physical health requires the intake of necessary nutrients and maintenance of proper nutrition. Therefore, we believe that good nutritional status is important for QOL. The present study found an association of each of "global health", "physical functioning", and "fatigue" with nutritional status. Pain, depression, fatigue, and anxiety tend to coexist during the treatment phase and have been reported to be related to HRQOL[32], which shows that nutritional status is an important foundation not only for physical health, but also in the "pain" and "emotional functioning" facets of mental health. In addition, an association has been reported between nutritional intake and memory function[33], suggesting that nutritional status may be related to "cognitive functioning".

It is debatable whether a statistically significant difference in QOL scores is clinically significant. Previous reports have stated that a difference in score of 10-15 should be considered clinically significant[18]. In addition, a more detailed report categorized clinical significance according to change in the average patient score, with a change of 5-10 points indicating "low-level" patients, 10-20 points for "moderate-level" patients, and 20 or more points for "high-level" patients, which allows in-

terpretation at different degrees of severity[34]. Applying this concept to the results of the present study, the results were clinically significant because there was a change in score of at least 10 points for all items, and of at least 20 points for some items.

A limitation of this study is the small number of cases. Long-term observation after transplantation in a larger number of cases is required in further studies and may yield different results from those obtained in the present study. Since the present study was limited to inpatients, we are currently conducting long-term follow-up on an outpatient basis to evaluate the impact of nutritional management methods that combine early intervention and long-term follow-up on improving QOL.

It is necessary to continue to validate early nutritional management for allo-HSCT patients, such as the nutritional management protocol implemented at our hospital. Enhancements to early nutritional management are expected to improve the quality of patient care.

The present findings indicate the importance of early nutritional management prior to transplantation, and they showed a trend toward better recovery of QOL scores after transplantation in patients who had received this intervention. Therefore, it is necessary to perform early intervention such as monitoring of nutrition and QOL scores pre-transplantation, as well as regular bilateral assessments long after discharge from hospital.

This study examined the association between pre- and post-transplantation nutritional indices and QOL in allo-HSCT patients. Energy and protein intakes were maintained throughout pre-transplantation, 30 days post-transplantation, 60 days post-transplantation, and discharge, all with adequate nutritional intakes. The results showed that maintaining good nutritional status before allo-HSCT may improve QOL after transplantation. To demonstrate the effectiveness of early nutritional management for the QOL of patients undergoing allo-HSCT, comparative studies of patients' QOL with and without nutritional intervention are needed.

In conclusion, early nutritional management of allo-HSCT patients prior to transplantation allowed maintenance of nutritional intake, and higher pre-transplant transthyretin levels were associated with higher QOL scores at 60 days post-transplantation.

Author Contributions

A.I. designed the study; developed the protocol; collected, analyzed, and interpreted the data; generated the figures and tables; and wrote the manuscript. T.T., E.T., Y.N., T.O., and A.K. participated in the design of the study and edited the final manuscript. The final manuscript was reviewed and approved by all authors.

Ethics approval

Approval was obtained from the Ethics Committee of Hamamatsu University School of Medicine to conduct this study (Approval No. 18-077).

Consent for publication

Consent was obtained on an opt-out basis.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

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