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Analysis

Impact of a Nutritional Risk Index on Clinical Outcomes after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Nutritional status is an important component of cancer care, and malnutrition itself can cause death in 10% to 20% of cancer patients. A nutritional risk index (NRI) is a useful tool for nutritional assessment of cancer patients. This study aimed to evaluate the impact of pretransplant NRI values on outcomes of allogeneic hematopoietic cell transplantation (allo-HSCT). One hundred sixty patients who underwent allo-HSCT between January 2008 and July 2017 at Konan Kosei Hospital were included in this single-center, retrospective analysis. NRI was calculated at the beginning of the conditioning regimen. The patients were divided into high NRI (NRI $\geq$ 97.5) and low NRI (NRI $<$ 97.5) groups, and overall survival (OS), nonrelapse mortality (NRM), and cumulative incidences of acute and chronic graft-versus-host disease (GVHD) were evaluated. Two-year OS rates were 76% (95% confidence interval [CI], 63% to 83%) and 50.4% (95% CI, 38% to 62%) in the high NRI and low NRI groups, respectively ($P < .001$). One-year cumulative incidences of NRM were 7.9% (95% CI, 3.5% to 15%) and 23% (95% CI, 14% to 33%; $P = .014$) and 2-year cumulative relapse rates were 17% (95% CI, 10% to 26%) and 32% (95% CI, 21% to 43%; $P = .10$) in the high NRI and low NRI groups, respectively. The multivariate analysis indicated low NRI was a significant risk factor for OS and NRM. Conversely, high NRI was associated with increased incidences of grades II to IV acute GVHD and chronic GVHD. Additionally, the subgroup analysis according to stem cell source revealed a significant benefit of higher NRI on survival only in umbilical cord blood recipients. Overall, these results suggest that pretransplant NRI might predict OS and NRM after allo-HSCT.

INTRODUCTION

Nutritional status is an important aspect of cancer care given that malnutrition is a cause of mortality in 10% to 20% of cancer patients [1]. In allogeneic hematopoietic stem cell transplantation (allo-HSCT) conditioning chemotherapy with or without total body irradiation (TBI) causes digestive symptoms such as anorexia, vomiting, and diarrhea, resulting in poor oral intake. In addition, post-transplant complications such as graft-versus-host disease (GVHD), transplant-associated thrombotic microangiopathy, and infection lead to deterioration of the nutritional status and can lead to long-term malnutrition after allo-HSCT [2].

Body weight (BW) and nitrogen balance were reported to be markedly reduced in the early period after allo-HSCT [3], and pretransplant malnutrition was found to lead to long-term malnutrition after allo-HSCT [2]. Pretransplant abnormalities in some nutrition-related markers, such as body mass index (BMI) [4–6], weight loss before allo-HSCT [7], serum albumin [8–11], and total serum protein [7], are associated with outcomes of allo-HSCT including overall survival (OS), nonrelapse mortality (NRM), and GVHD. However, none of the described markers reflects the nutritional status of the patient directly, and the relationship between nutritional status and outcomes of allo-HSCT remains ambiguous.

The nutritional risk index (NRI), initially proposed by Buzby et al. for evaluating nutritional status of preoperative patients on total parenteral nutrition [12,13], has become a useful tool for nutritional assessment of cancer patients [14]. Importantly, Bouillanne et al. [15] introduced a geriatric NRI for hospitalized elderly patients that was easy to calculate using parameters at a single time point including ideal BW (IBW) instead of usual BW (mean BW over a 6-month period) used in the calculation of NRI. Thereafter, a modified NRI using IBW was applied to evaluate the condition of patients to predict clinical outcomes in various situations, including perioperative cancer patients [16,17], ambulatory patients before admission [18], patients with advanced heart failure [19], those with chronic kidney disease facing dialysis [20], and patients with schizophrenia [21].

Patients undergoing allo-HSCT become undernourished during the long peritransplant period and in many cases need

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temporary total parenteral nutrition. These circumstances resemble the perioperative period; therefore, we hypothesized that assessment of the nutritional status by the NRI should aid in the prediction of outcomes of allo-HSCT. This study aimed to evaluate the impact of pretransplant NRI on allo-HSCT outcomes.

METHODS

Patients

All adult patients who underwent first allo-HSCT between January 2008 and July 2017 at Konan Kosei Hospital were included in this study. Patients who underwent any prior allo-HSCT were excluded, whereas patients who underwent prior autologous HSCT were included. Written informed consent was obtained from all eligible patients. The study was approved by the institutional ethics committee of Konan Kosei Hospital.

Data Collection

Data on serum albumin concentration (g/L) and BW (kg) were retrospectively collected from the medical records at the nearest time point before the conditioning regimen and at 30 and 60 days after allo-HSCT. If BW was not available from the same day of serum albumin measurement, the nearest available BW value before the serum albumin measurement was used to calculate the NRI. Height obtained on the day of admission for allo-HSCT was used for all calculations.

NRI and Related Indices

NRI was calculated as follows: $(1.519 \times \text{serum albumin}) + (41.7 \times \text{current BW/IBW})$ [17,19]. In this study IBW was calculated according to the Lorentz formula, with height in centimeters: for men, IBW = height − 100 − (height − 150)/4; for women, IBW = height − 100 − (height − 150)/2.5 [15]. When current BW exceeded IBW, we set the current BW/IBW to 1, in line with previous reports [15]. Risk stratification of malnutrition was as follows: normal risk (NRI $\geq$ 100), mild risk (97.5 $\leq$ NRI $<$ 100), moderate risk (83.5 $\leq$ NRI $<$ 97.5), and severe risk (NRI $<$ 83.5) [17]. We set NRI $<$ 97.5 to indicate clinically significant malnourishment according to previous reports [13,16,18]. Percent IBW was defined as current BW/IBW $\times$ 100.

Definitions

Patients were divided into high NRI (NRI $\geq$ 97.5) and low NRI (NRI $<$ 97.5) groups according to the NRI score.

Disease risk was classified according to the refined disease risk index proposed by Armand et al. [22]. Hematopoietic cell transplant–specific comorbidity index (HCT-CI) was scored according to Sorror et al. [23].

The myeloablative and reduced-intensity conditioning regimens were defined according to the criteria of the National Marrow Donor Program/Center for International Blood and Marrow Transplant Research operational definitions [24].

Acute GVHD (aGVHD) was diagnosed and graded according to established criteria [25,26]. Chronic GVHD (cGVHD) was diagnosed as described previously [27] and categorized into severe and other cGVHD that included mild and moderate cGVHD.

Endpoints

Study endpoints were OS, NRM, and relapse rate. OS was defined as the time from transplant to death from any cause, and NRM was defined as death without recurrence of underlying disease after HSCT. Time to relapse was calculated as the time from transplant to the recurrence of underlying hematologic malignant disease. One hundred fifty-seven patients with malignant disease were included in the analysis of relapse, whereas 3 patients with aplastic anemia classified as "others" were excluded from the relapse analysis. For those who did not achieve complete remission during the study period, day 1 after the allo-HSCT was designated as the date of relapse. Cumulative incidences of grades II to IV and grades III to IV aGVHD and all-grade or severe cGVHD were also assessed. Organs and sites involved in aGVHD of any stage and cGVHD of any score were assessed to determine cumulative incidences.

We also assessed time to neutrophil engraftment, day of first discharge after allo-HSCT, and absolute lymphocyte count on day 60 after allo-HSCT as secondary endpoints. The day of neutrophil engraftment was defined as the first day of 3 consecutive measurements reaching a neutrophil count of at least $.5 \times 10^9$/L.

Statistical Analyses

All statistical analyses were performed using EZR version 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [28]. Two-sided $P < .05$ were considered to be statistically significant.

The regression analysis between the NRI and related indices was performed with Spearman's correlation analysis. The Mann-Whitney U test and Fisher exact test were used for statistical analyses on continuous and

Table 1
Patient Characteristic

Variables	Low NRI Group (n = 71)	High NRI Group (n = 89)	*P*
Age, yr			
≤50	27 (38.0)	51 (57.3)	.02
>50	44 (62.0)	38 (42.7)	
Sex			
Female	32 (45.1)	27 (30.3)	.07
Male	39 (54.9)	62 (69.7)	
Disease			
AML	45 (63.4)	44 (49.4)	.14
ALL	2 (2.8)	15 (16.9)	
MDS	8 (11.3)	12 (13.5)	
CML	2 (2.8)	3 (3.4)	
ML	5 (7.0)	6 (6.7)	
ATLL	5 (7.0)	4 (4.5)	
Others*	4(5.6)	5 (5.6)	
rDRI			
Low	7 (9.9)	14 (15.7)	.052
Intermediate	32 (45.1)	49 (55.1)	
High	22 (31.0)	23 (25.8)	
Very high	10 (14.1)	3 (3.4)	
Stem cell source			
BM	33 (46.5)	33 (37.1)	.24
PBSCs	9 (12.7)	20 (22.5)	
UCB	29 (40.8)	36 (40.4)	
Related donor			
Yes	11 (15.5)	18 (20.2)	.54
No	60 (84.5)	71 (79.8)	
HLA			
Match	35 (49.3)	42 (47.2)	.98
Mismatch	8 (11.3)	11 (12.4)	
UCB	28 (39.4)	36 (40.4)	
HCT-CI			
0	32 (45.1)	46 (51.7)	.32
1-2	20 (28.2)	28 (31.5)	
≥3	19 (26.8)	15 (16.9)	
Prior autologous HSCT			
No	70 (98.6)	87 (97.8)	1.00
Yes	1 (1.4)	2 (2.2)	
Myeloablative conditioning			
No	26 (36.6)	19 (21.3)	.04
Yes	45 (63.4)	70 (78.7)	
TBI			
No	32 (45.1)	27 (30.3)	.02
Low	19 (26.8)	18 (20.2)	
High (≥8 Gy)	20 (28.2)	44 (49.4)	
GVHD prophylaxis			
PostCY/TAC/MMF	1 (1.4)	1 (1.1)	.71
CsA	8 (11.3)	12 (13.5)	
TAC	62 (87.3)	76 (85.3)	

Values are n (%). AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ML, malignant lymphoma; ATLL, adult T cell leukemia/lymphoma; rDRI, refined disease risk index; CY, cyclophosphamide; TAC, tacrolimus; MMF, mycophenolate mofetil; CsA, cyclosporine.

* Others include 3 patients with aplastic anemia, 4 patients with multiple myeloma, 1 patient with primary myelofibrosis, and 1 patient with chronic active Epstein-Barr virus infection.

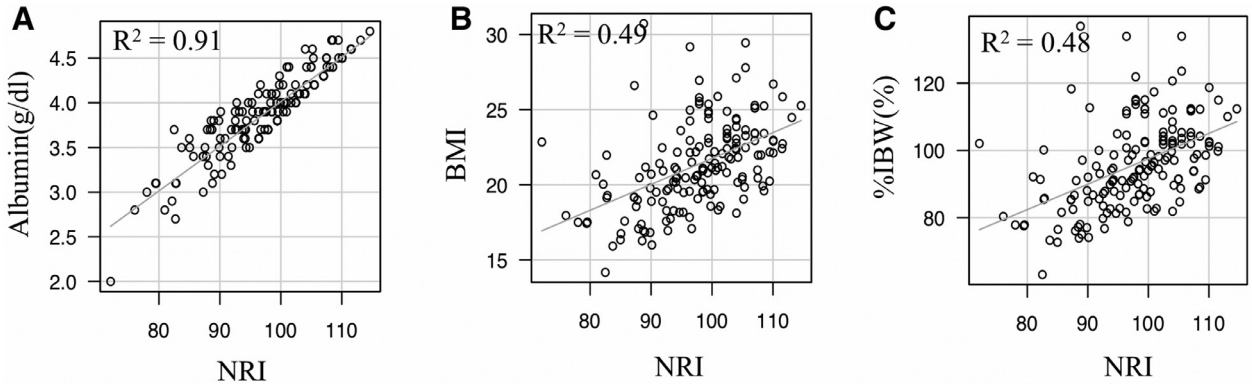

Figure 1. Correlations of NRI with other indices. NRI was strongly correlated with serum albumin concentration (A) and mildly correlated with BMI (B) and %IBW (C).

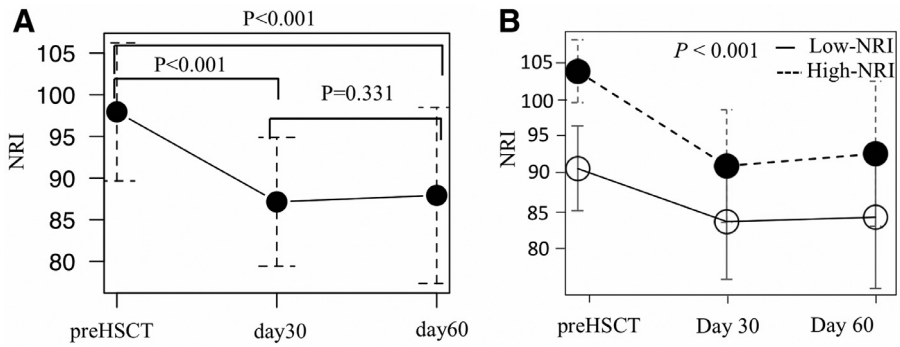

Figure 2. Time-dependent changes in NRI. (A) NRI significantly declined after allo-HSCT. (B) The high NRI and low NRI groups exhibited similar changes.

Table 2
Nutrition-Related Indices

Index	Total	Low NRI	High NRI	*P* value
	(N = 160)	(n = 71) median (range)	(n = 89) median (range)	
NRI	98.5	91.4	104	<.001
	(72.1-115)	(72.1-97.4)	(97.6-115)	
BMI, kg/m^2	21.1	19.6	22.4	<.001
	(14.2-30.7)	(14.2-30.7)	(18.1-29.5)	
%IBW	94.3	87.2	101	<.001
	(63.1-137)	(63.1-137)	(81.9-134)	
Albumin, g/dL	3.9	3.6	4.1	<.001
	(2.0-4.8)	(2.0-4.2)	(3.7-4.8)	

Values are median (range).

categorical variables. The univariate probability of OS was estimated using the Kaplan-Meier method and compared between 2 groups using the log-rank test. Differences in cumulative incidences of relapse, NRM, aGVHD, and cGVHD, including organ-specific analyses, in the presence of competing events were examined with Gray's test. When the competing risk analysis was performed, relapse was the competing event for NRM, and NRM was the competing event for relapse. For aGVHD or cGVHD, death without these complications was considered as the competing event. In multivariate analysis the Cox proportional hazards model was used for OS, and the Fine-Gray model was used for relapse and NRM by selecting covariates by a backward selection among variables with a $P < .1$ in the univariate analysis. Comparisons among multiple groups were performed using the post hoc Bonferroni comparison test.

RESULTS

Patient Characteristics

From January 2008 to July 2017, 160 patients underwent allo-HSCT at Konan Kosei Hospital. The median follow-up duration from allo-HSCT was 719 days (range, 1 to 3609), and 64 patients died during the study period. There were 71 and 89 patients in the low NRI and high NRI groups, respectively. The baseline characteristics of patients in 2 groups are shown in Table 1. Briefly, patients in the low NRI group were significantly older and had a tendency to have a higher refined disease risk index and a higher HCT-CI score.

Evaluation of the NRI

By regression analysis, the NRI was strongly correlated with serum albumin (R^2 = .91) and weakly with BMI and %IBW (R^2 = .49 and .48, respectively) (Figure 1). The NRI declined significantly until 30 days after allo-HSCT and plateaued (Figure 2A). The mean NRI score was higher in the high NRI group at all time points, whereas both groups showed similar time-dependent changes after allo-HSCT (Figure 2B).

NRI and other nutrition-related indices are shown in Table 2. All indices were significantly higher in the high NRI group.

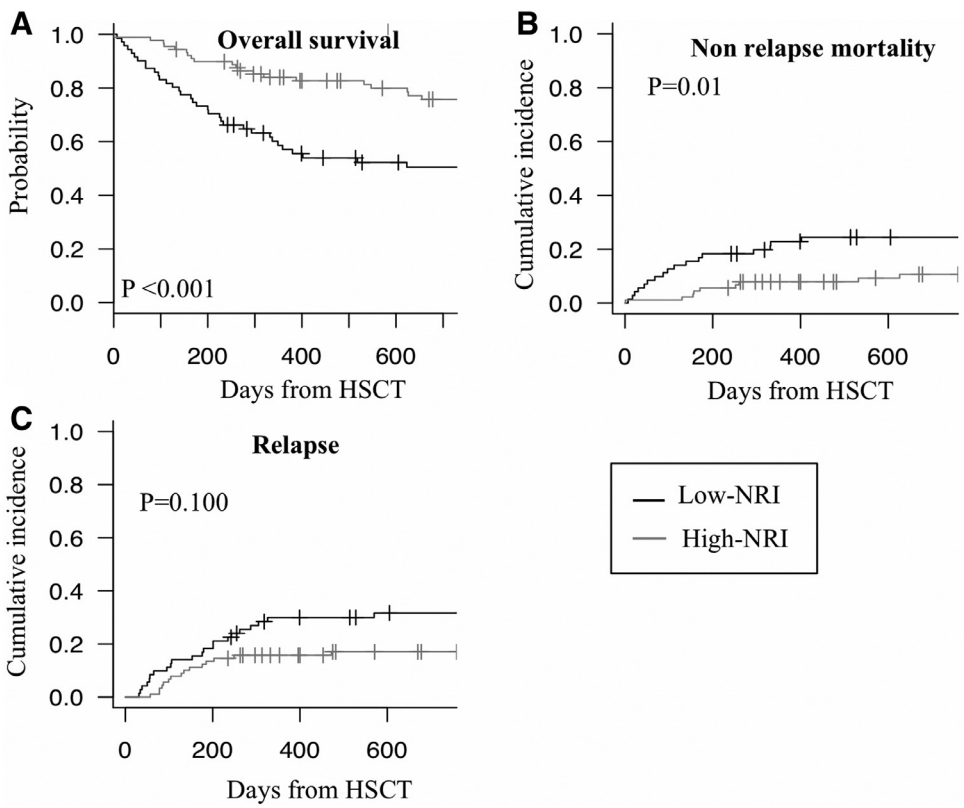

Figure 3. Probabilities of OS (A), cumulative incidences of NRM (B), and cumulative incidences of relapse (C) in the high NRI and low NRI groups.

OS, NRM, and Relapse

The 2-year OS rates were 76% (95% confidence interval [CI], 63% to 83%) in the high NRI group and 50.4% (95% CI, 38% to 62%) in the low NRI group ($P < .001$) (Figure 3A). The 1-year cumulative incidences of NRM were 7.9% (95% CI, 3.5% to 15%) and 23% (95% CI, 14% to 33%; $P = .01$) (Figure 3B) in the high NRI and low NRI groups, respectively. Furthermore, the 2-year cumulative incidences of relapse were 17% (95% CI, 10% to 26%) and 32% (95% CI, 21% to 43%; $P = .10$) (Figure 3C) in the high NRI and low NRI groups, respectively.

Univariate and multivariate analyses of risk factors for OS and NRM are shown in Tables 3 and 4, respectively. Low NRI score (<97.5), high disease risk (high and very high refined disease risk index), and high HCT-CI score (≥3) were significant risk factors for OS in the multivariate analysis. Additionally, low NRI score (<97.5) and high HCT-CI score (≥3) were independent risk factors for NRM. Causes of NRM are summarized in Table 5. In the study cohort 28 patients, including 19 patients in the low NRI group, died from causes other than relapse. The most common cause of NRM was noninfectious

Table 3
Univariate Analysis for OS and NRM

	OS		NRM	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, yr				
<50	1		1	
≥50	1.89 (1.14-3.14)	.01	2.82 (1.24-6.38)	.01
rDRI				
Low	1		1	
Intermediate	1.92 (.67-5.55)	.22	2.20 (.50-9.71)	.30
High	4.79 (1.66-13.8)	.004	3.14 (.67-14.7)	.15
Very high	9.46 (2.95-30.4)	<.001	6.51 (1.18-36.1)	.03
HCT-CI				
0	1		1	
1-2	1.65 (.92-2.97)	.09	2.53 (1.02-6.29)	.046
≥3	2.41 (1.32-4.41)	.004	3.79 (1.49-9.69)	.005
NRI				
High	1		1	
Low	2.37 (1.43-3.91)	<.001	2.58 (1.21-5.47)	.01

HR indicates hazard ratio.

Table 4
Multivariate Analysis for OS and NRM

	OS		NRM	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, yr				
<50	—		1	
≥50	—		2.30 (1.00-5.30)	.052
rDRI				
Low	1		—	
Intermediate	2.09 (.72-6.05)	.17	—	
High	4.41 (1.52-12.8)	.006	—	
Very high	9.02 (2.74-29.6)	<.001	—	
HCT-CI				
0	1		1	
1-2	1.33 (.72-2.45)	.36	2.42 (.97-6.07)	.06
≥3	2.43 (1.31-4.50)	.006	3.61 (1.40-9.32)	.008
NRI				
High	1		1	
Low	2.13 (1.28-3.55)	.004	2.28 (1.05-4.94)	.04

Table 5
Causes of NRM

	Low NRI Group (n =19)	High NRI Group (n = 9)
Noninfectious pulmonary complications	5 (26.3)	3 (33.3)
TA-TMA	5 (26.3)	2 (22.2)
Hemorrhagic cystitis	2 (10.5)	1 (11.1)
Sepsis	1 (5.3)	2 (22.2)
Intracerebral hemorrhage	2 (10.5)	0 (0)
Veno-occlusive disease	2 (10.5)	0 (0)
Heart failure	0 (0)	1 (11.1)
Hemophagocytic lymphohistiocytosis	1 (5.3)	0 (0)
Donor-derived leukemia	1 (5.3)	0 (0)

Values are n (%). TA-TMA indicates transplant associated-thrombotic microangiopathy.

pulmonary complications followed by transplant-associated thrombotic microangiopathy. Both complications tended to be more frequent in the low NRI group. Patients who developed intracerebral hemorrhage and veno-occlusive disease were only observed in the low NRI group.

The detailed stratification of OS, NRM, and relapse rates according to the NRI are shown in Figure 4. The 2-year OS rates were 74% (95% CI, 61% to 84%), 84% (95% CI, 62% to 94%), 51% (95% CI, 38% to 64%), and 36% (95% CI, 11% to 63%) for normal-risk, mild-risk, moderate-risk, and severe-risk groups, respectively ($P = .001$). Additionally, the 1-year cumulative incidences of NRM were 6.3% (95% CI, 2.0% to 14%), 12% (95% CI, 2.9% to 28%), 22% (95% CI, 12% to 34%), and 27% (95% CI, 5.8%-55%) for normal-risk, mild-risk, moderate-risk, and severe-risk groups, respectively ($P = .15$), whereas the 2-year cumulative incidences of relapse for normal-risk, mild-risk, moderate-risk, and severe-risk groups were 19% (95% CI, 10% to 30%), 12% (95% CI, 2.9% to 28%), 31% (95% CI, 19% to 43%), and 36% (95% CI, 10% to 65%), respectively ($P = .35$). Although not significant by post hoc analysis, patients in the mild-risk group had the highest OS rate and the lowest incidence of relapse.

Graft-versus-Host Disease

Cumulative incidences of grades II to IV aGVHD at 100 days after allo-HSCT were 44% (95% CI, 33% to 54%) and 21% (95% CI, 13% to 32%) in the high NRI and low NRI groups, respectively ($P = .02$) (Figure 5A). The cumulative incidences of grades III to IV aGVHD at 100 days were 6.8% (95% CI, 2.8% to 13%) and 4.2% (95% CI, 1.1% to 11%) in the high NRI and low NRI groups, respectively ($P = .78$) (Figure 5B).

The cumulative cGVHD incidences at 4 years were 55% (95% CI, 43% to 65%) for the high NRI group and 34% (95% CI, 23% to 46%) for the low NRI group ($P = .03$) (Figure 5C). Cumulative incidences of severe cGVHD at 4 years were 13% (95% CI, 6.4% to 21%) for the high NRI group and 13% (95% CI, 6.0% to 24%) for the low NRI group ($P = .99$) (Figure 5D). The organs and sites involved in aGVHD and cGVHD according to the NRI are shown in Table 6. The skin involvement during aGVHD and cGVHD was significantly more frequent in the high NRI group compared with the low NRI group.

Secondary Endpoints

As shown in Table 7, the NRI was not associated significantly with neutrophil engraftment, day of discharge, or absolute lymphocyte count on day 60 after allo-HSCT. However, there was a weak tendency of earlier discharge in the high NRI group.

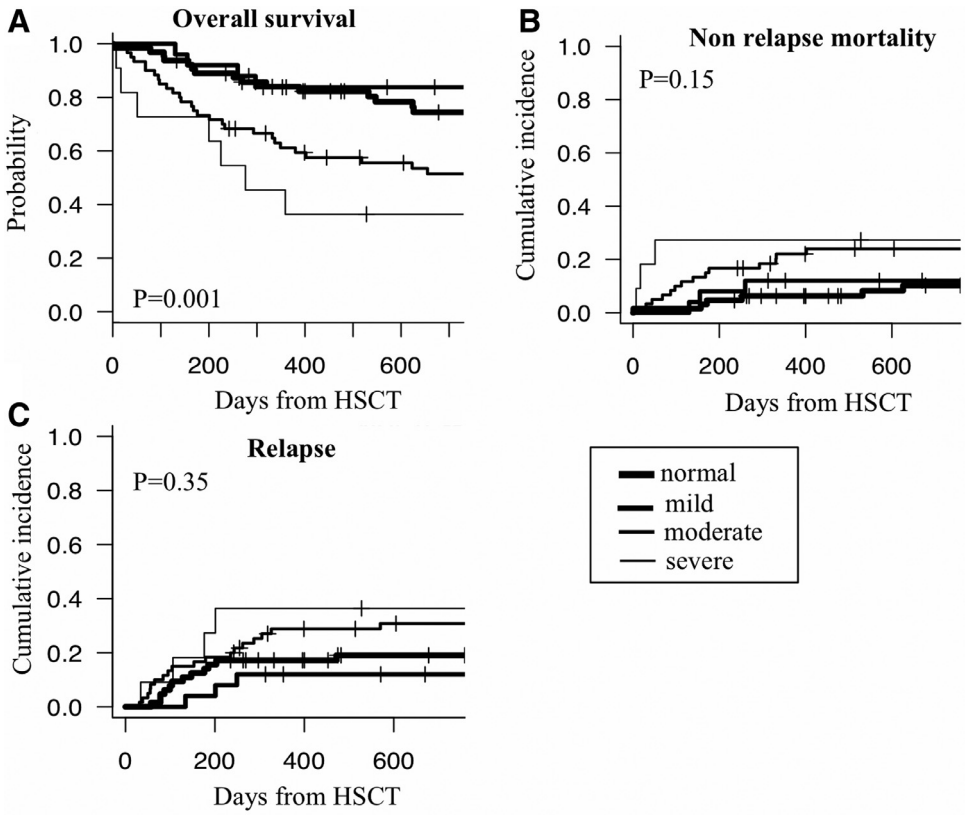

Figure 4. Probabilities of OS (A), cumulative incidences of NRM (B), and cumulative incidences of relapse (C) in 4 groups stratified by the NRI.

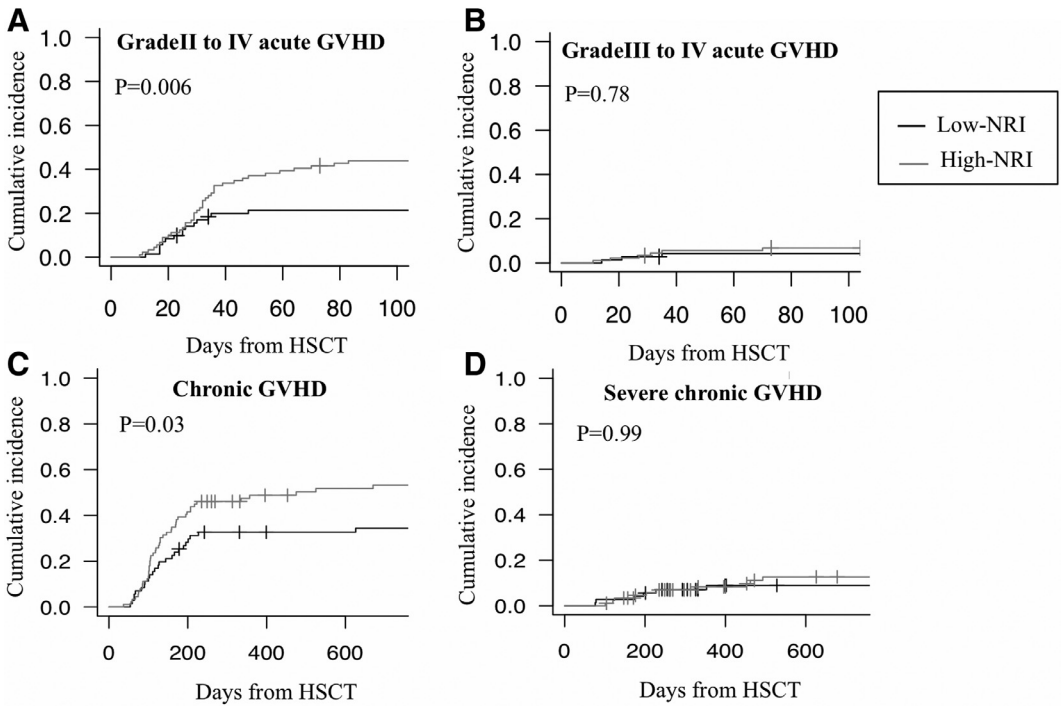

Figure 5. Cumulative incidences of grades II to IV (A) and grades III to IV (B) aGVHD and all-grade (C) and severe (D) cGVHD in the high NRI and low NRI groups.

Table 6
Cumulative Incidences of aGVHD and cGVHD in Each Organ

Organ	Low NRI Group (n = 71)	High NRI Group (n = 89)	*P*
aGVHD 100 days cumulative incidence			
Skin	46.5 (34.5-57.6)	70.8 (60.0-79.2)	.003
Gut	12.7 (6.2-21.6)	14.6 (8.2-22.8)	.76
Liver	2.8 (.5-8.8)	3.4 (.9-8.7)	.84
cGVHD 4-year cumulative incidence			
Skin	20.2 (11.6-30.5)	39.3 (28.8-49.6)	.01
Oral	20.1 (11.6-30.4)	29.3 (20.2-39.1)	.14
Gut	1.4 (.1-6.8)	1.1 (.1-5.5)	.87
Liver	11.3 (5.2-20.0)	18.1 (10.9-26.9)	.25
Lung	5.0 (1.2-12.9)	2.4 (.5-7.8)	.30

Values in parentheses are 95% CIs.

Table 7
Secondary Endpoints

Variable	Low NRI Group (n = 71)	High NRI Group (n = 89)	*P*
Engraftment, day	17 (11-43)	17 (10-36)	.84
Discharge, day	85 (44-255)	73 (36-250)	.12
ALC on day 60, /μL	930 (74-3654)	1011 (96-3552)	.86

Values are median (range). ALC indicates absolute leukocyte count.

Subgroup Snalysis

We performed analyses of subgroups according to the stem cell source (Figure 6). Among patients receiving bone marrow (BM) or peripheral blood stem cells (PBSCs), the 2-year OS rates were 74% (95% CI, 59% to 84%) and 50% (95% CI, 34% to 64%) in the high NRI and low NRI groups, respectively ($P = .054$) (Figure 6A). Conversely, among patients receiving umbilical cord blood (UCB), the 2-year OS rates were 79% (95% CI, 60% to 89%) and 51% (95% CI, 32% to 68%) in the high NRI and low NRI groups, respectively ($P = .001$) (Figure 6B).

Among patients receiving BM or PBSCs, the 1-year cumulative incidences of NRM were 9.4% (95% CI, 3.4% to 19%) and 24% (95% CI, 12% to 38%) in the high NRI and low NRI groups, respectively ($P = .20$) (Figure 6C). In contrast, among patients receiving UCB, the 1-year cumulative incidences of NRM were 5.7% (95% CI, 1.0% to 17%) and 21% (95% CI, 8.2% to 38%) in the high NRI and low NRI groups, respectively ($P = .03$) (Figure 6D). Furthermore, for those patients receiving BM or PBSCs, the 2-year cumulative incidences of relapse were 17% (95% CI, 8.4% to 29%) and 29% (95% CI, 16% to 43%) for each group, respectively ($P = .40$) (Figure 6E), whereas for UCB, those values were 17% (95% CI, 6.6% to 31%) and 35% (95% CI, 18% to 53%) for each group, respectively ($P = .15$) (Figure 6F).

Figure 7 shows the cumulative incidences of aGVHD and cGVHD according to the stem cell source. Among patients receiving BM or PBSCs, the 100-day cumulative incidences of grades II to IV aGVHD were similar between the high NRI and the low NRI groups (38% [95% CI, 25% to 51%] and 24% [95% CI, 12% to 38%], respectively; $P = .26$) (Figure 7A). In contrast, among patients receiving UCB, the 100-day cumulative incidence of grades II to IV aGVHD was higher in the high NRI group than in the low NRI group (53% [95% CI, 35% to 68%] versus 17% [95% CI, 6.2% to 33%]; $P = .02$) (Figure 7B). There was no difference in the 100-day cumulative incidences of grades III to IV aGVHD between the high NRI and the low NRI groups based on stem cell source, which were 7.6% (95% CI, 2.4% to 17%) and 4.8% (95% CI, .8% to 14%), respectively, in patients receiving BM or PBSCs ($P = .57$) (Figure 7C) and 5.6% (95% CI, 1.0% to 17%) and 3.4% (95% CI, .2% to 15%), respectively, in patients receiving UCB ($P = .81$) (Figure 7D).

Among patients receiving BM or PBSCs, the 4-year cumulative incidences of cGVHD were similar between the high NRI and the low NRI groups (55% [95% CI, 41% to 68%] and 43% [95% CI, 28% to 57%], respectively; $P = .46$) (Figure 7E). In

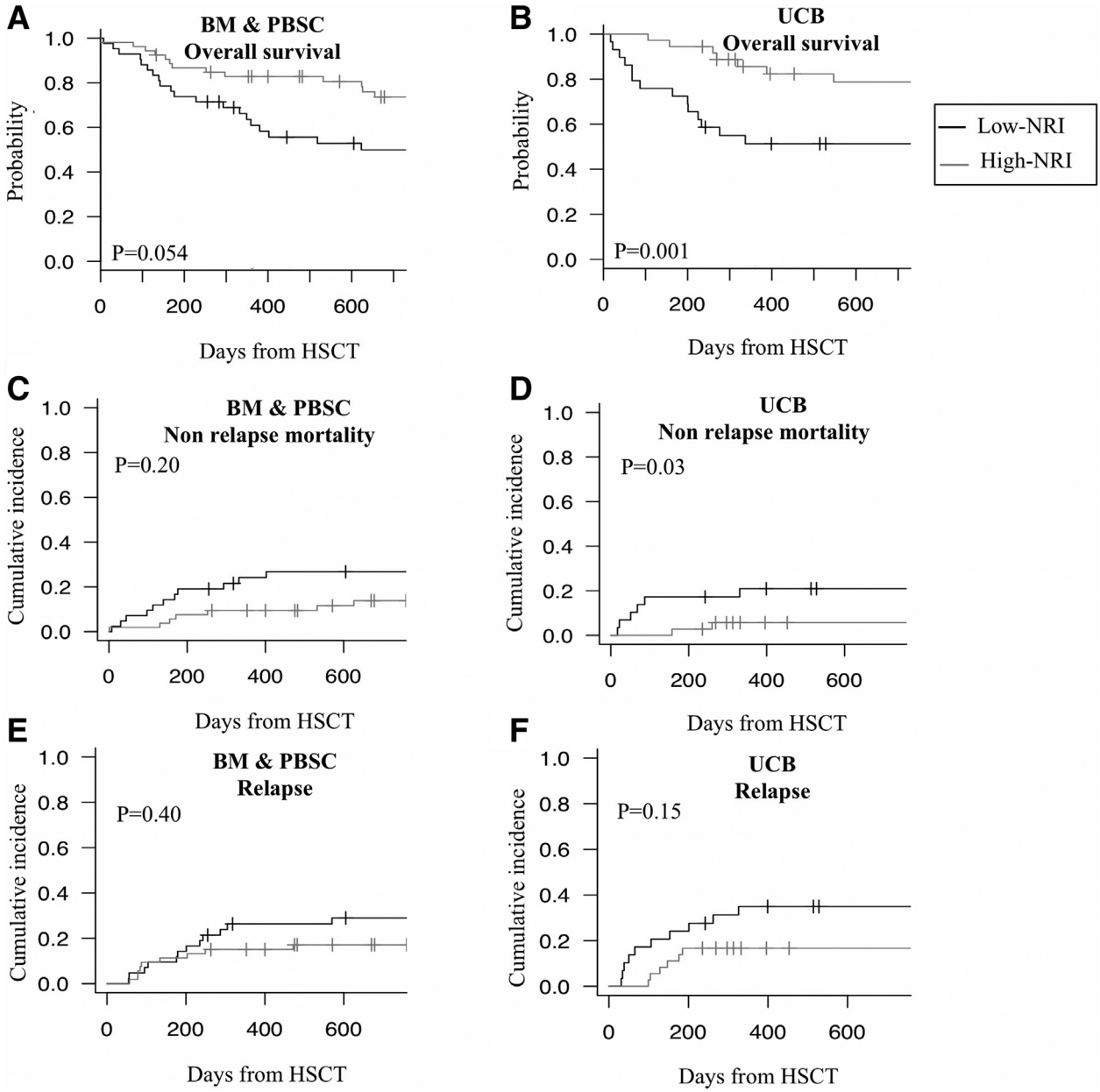

Figure 6. Probabilities of OS among recipients of BM and PBSCs (A) and those of UCB (B), cumulative incidences of NRM among recipients of BM and PBSCs (C) and those of UCB (D), and cumulative incidences of relapse among recipients of BM and PBSCs (E) and those of UCB (F), according to the NRI.

contrast, among patients receiving UCB, the 4-year cumulative incidence of cGVHD was higher in the high NRI group than in the low NRI group (52% [95% CI, 33% to 68%] and 23% [95% CI, 8.7% to 42%], respectively; $P = .01$) (Figure 7F). However, there was no difference in the 4-year cumulative incidences of severe cGVHD between the high NRI and the low NRI groups based on stem cell source, which were 20% (95% CI, 10% to 32%) and 16% (95% CI, 6.3% to 31%), respectively, in patients receiving BM or PBSCs ($P = .57$) (Figure 7G) and .0% (95% CI, .0% to .0%) and 9.3% (95% CI, 1.3% to 27%), respectively, in patients receiving UCB ($P = .14$) (Figure 7H).

DISCUSSION

In the current study we found that the NRI was associated with allo-HSCT outcomes, including OS and NRM. To our knowledge, this is the first original report elucidating NRI in patients undergoing allo-HSCT. We showed that a low NRI was associated with inferior OS accompanied with an increased incidence of NRM and that the NRI was useful in predicting allo-HSCT outcomes.

The NRI, a simple index calculated using a combination of serum albumin concentration and BW (current BW/IBW), might be a better indicator of the real nutritional status compared with individual variables. The NRI is calculated using serum albumin, BW, and IBW and is strongly affected by serum albumin. Artz et al. [9] showed that hypoalbuminemia before allo-HSCT was associated strongly with inferior survival and higher incidence of NRM. Serum albumin concentration, albeit crudely reflecting nutritional status [9], is not considered a good parameter for determining nutritional status because it can be affected by inflammation or edema [29]. Conversely, the impact of BW on outcomes after allo-HSCT remains controversial. Nakao et al. [30] indicated that being

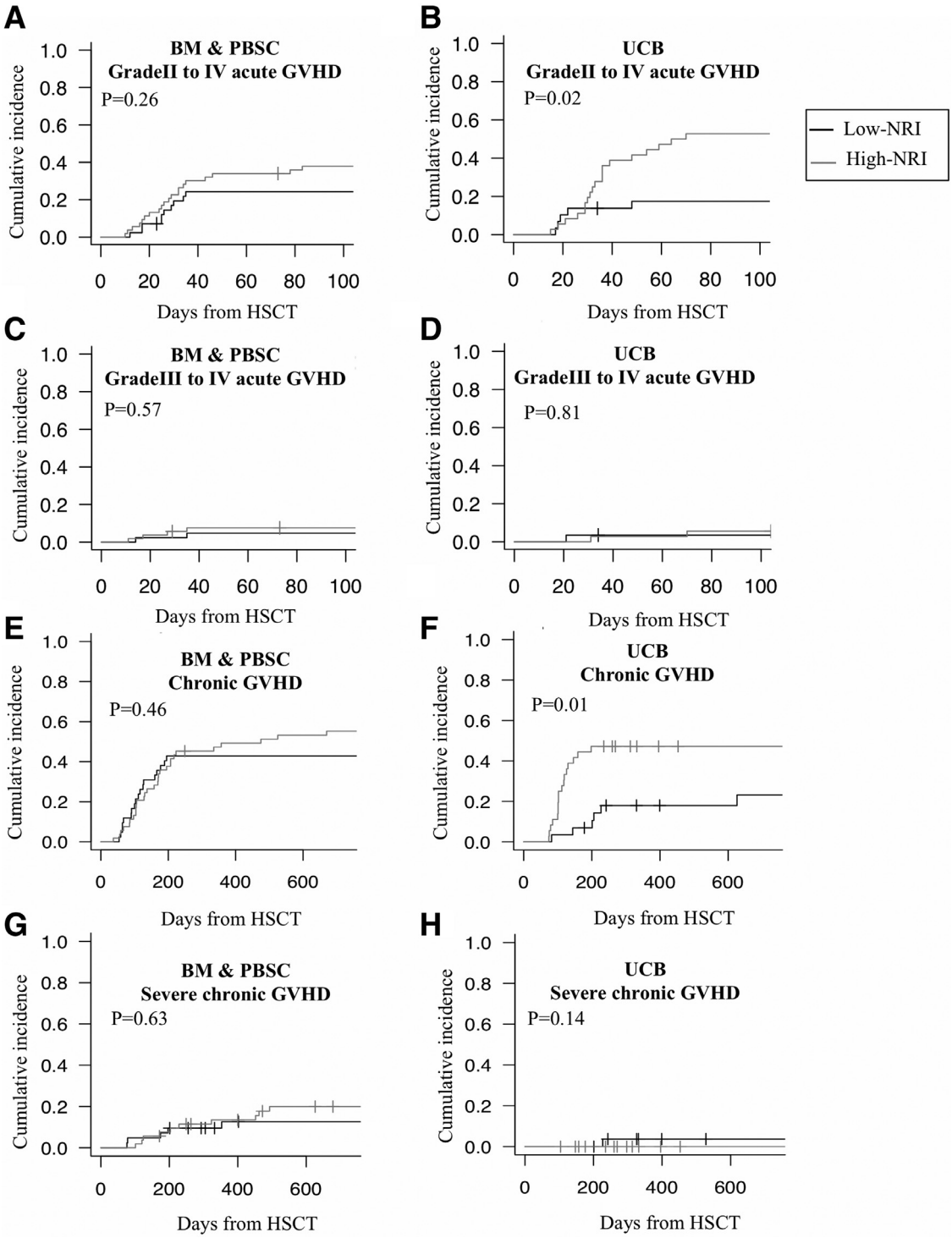

Figure 7. Cumulative incidences of grades II to IV aGVHD among recipients of BM and PBSCs (A) and those of UCB (B), grades III to IV aGVHD among recipients of BM and PBSCs (C) and those of UCB (D), all-grade cGVHD among recipients of BM and PBSCs (E) and those of UCB (F), and severe cGVHD among recipients of BM and PBSCs (G) and those of UCB (H), according to the NRI.

overweight before transplant was associated with inferior OS in a meta-analysis; however, the effect of underweight was not assessed. Other studies showed that underweight assessed by BMI [5] or %IBW [4] had a negative impact on OS after allo-HSCT. Underweight is recognized as a surrogate marker of malnutrition as well as hypoalbuminemia, whereas overweight does not necessarily reflect a good nutritional status but may simply indicate obesity or edema. Because the actual BW/IBW was set to a value of 1 in patients whose actual BW exceeded IBW, the influence of overweight in the NRI determination was eliminated. In contrast, underweight clearly led to lower NRI scores and had a negative impact on survival. Overweight with edema in malnourished patients resulted in lower NRI scores because of low serum albumin concentrations. Conversely, an erroneous increase in serum albumin concentrations in patients with dehydration might be balanced by underweight in NRI determination.

An NRI of 97.5, which was commonly used as the cut-off value for malnutrition in previous studies [16,18], was used for stratification of patients undergoing allo-HSCT. The median NRI of the entire cohort of 160 patients was 98.5, and patients were divided into 2 roughly balanced groups, including 71 patients (44.4%) in the low NRI group and 89 patients (55.6%) in the high NRI group, based on the cut-off NRI of 97.5. Further analysis of the patients based on stratification into 4 risk groups according to the NRI revealed that the highest OS probability was observed in patients with mild risk, although there was no significant difference compared with those patients with normal risk. Conversely, the probabilities of OS were similar between moderate-risk and severe-risk patients and significantly lower than those for normal-risk and mild-risk patients. These data suggested that stratification by an NRI of 97.5 was valid in the setting of allo-HSCT similar to other settings reported in previous studies [18,31,32].

In the current cohort causes of NRM were diverse, and the rate of each cause was small, hindering our ability to identify a specific pathophysiology associated with low NRI values.

Regarding GVHD, our analysis also showed that higher NRI was associated with increased incidences of grades II to IV aGVHD and all-grade cGVHD, whereas grades III to IV aGVHD and severe cGVHD were not associated with the NRI. Although the influence of obesity or overweight on aGVHD and cGVHD was reported in various settings [5,33,34], Nakao et al. [30] showed that overweight was associated with a high incidence of aGVHD by a meta-analysis, whereas another study showed that the peritransplant decline in serum albumin was associated with severe aGVHD [35]. Thus, nutritional status may be associated with the occurrence and severity of GVHD, although the issue remains controversial. Various factors other than nutritional status might also be associated with GVHD; TBI was reported to be significantly associated with aGVHD, especially skin and gastrointestinal aGVHD [36]. Similarly, the use of TBI-containing conditioning regimens was significantly associated with grades II to IV aGVHD and skin aGVHD in the current study (date not shown). Although not statistically significant, patients in the high NRI group underwent TBI-containing conditioning regimens more frequently than those in the low NRI group in the current cohort; this difference might contribute to the incidence of mild aGVHD to some extent.

In a subgroup analysis according to stem cell sources, the significant benefit of a higher NRI score on survival was observed only among the recipients of UCB. Furthermore, the significantly higher incidences of grades II to IV aGVHD and all-grade cGVHD and the lower incidence of NRM in the high NRI group were observed only among the recipients of UCB. In a retrospective study of the Japanese national registry data, grades I to II aGVHD and limited cGVHD were shown to be associated with lower NRM and overall mortality [37]. Therefore, the high incidence of mild GVHD in the high NRI group might have contributed to lower NRM and better OS rates, although the underlying relationship between higher NRI scores and higher incidences of mild GVHD was unclear. Another possible explanation of the better outcomes observed in the high NRI group among the recipients of UCB should also be considered: A good pretransplant nutritional status might overcome poor post-transplant nutritional status induced by prolonged infection and mucosal damage due to slower hematologic recovery in UCB transplant compared with transplant using other stem cell sources.

The present study has several important limitations. First, this was a single-center retrospective cohort study. Although we found low NRI values as a risk factor for OS and NRM consistently after adjustment for confounders by multivariate analysis, the study design, patient backgrounds, and transplant procedures might affect the results. Moreover, the small number of patients in the subgroup analysis limited the interpretation of the results. Second, the NRI, which was originally calculated using usual BW over 6 months, was calculated using IBW in the current study because many patients were referred for allo-HSCT from other institutes and usual BW was not available in most cases. In NRI calculation, we used IBW instead of usual BW following the methods described by Bouillanne et al. [15] and Oluwayemisi et al. [19]; however, some underlying inconsistency could not be denied. Additionally, the cut-off points for stratification by the NRI, which were based on previous reports [16,18], should be validated by receiver operating curve analysis in larger cohorts of patients undergoing allo-HSCT. Our findings need to be explored further by multicenter studies, and studies addressing pretransplant nutritional interventions are also needed.

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