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Cord Blood

The Prognostic Impact of Pretransplantation Inflammatory and Nutritional Status in Adult Patients after Myeloablative Single Cord Blood Transplantation

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Markers of inflammatory and nutritional status, such as the Controlling Nutritional Status (CONUT) score, Prognostic Nutritional Index, Glasgow Prognostic Score, and C-reactive protein-albumin ratio (CAR) has been demonstrated to be associated with poor prognosis in patients with various cancers. Although the relatively low cell dose of a single cord blood unit restricts the indication for cord blood transplantation (CBT) to pediatric and relatively smaller and lighter adult patients, the impact of malnutrition on outcomes after CBT is unclear. We retrospectively analyzed 165 adult patients who underwent myeloablative single-unit CBT in our institute. In multivariate analysis, a higher CONUT score, which is indicative of poor inflammatory and nutritional status, was significantly associated with poor outcomes, including low neutrophil engraftment and development of extensive chronic graft-versus-host disease. A higher CAR, which is also suggestive of poor inflammatory and nutritional status, was significantly associated with poor neutrophil engraftment and higher overall mortality. Body mass index (BMI) was not associated with transplantation outcomes. These data suggest that poor pretransplantation inflammatory and nutritional status might be a more practical parameter than lower BMI, for predicting transplantation outcomes after single CBT for adults.

INTRODUCTION

Cord blood transplantation (CBT) is an acceptable alternative donor source for patients who are candidates for allogeneic hematopoietic cell transplantation (HCT) but lack suitable HLA-matched related or unrelated donors [1-6]. The limited cell dose based on the body weight of the patient is associated with engraftment failure and mortality after single CBT [7-9], particularly in adults. Therefore, the relatively low cell dose in a single cord blood unit restricts the indication for CBT to pediatric and relatively smaller and lighter adult patients.

Recently, inflammatory and nutritional status, as measured by such parameters as the Controlling Nutritional Status (CONUT) score, Prognostic Nutritional Index (PNI), Glasgow Prognostic Score (GPS), and C-reactive protein (CRP)-albumin ratio (CAR), has been demonstrated to be associated with poor prognosis and postoperative complications in patients with various cancers who receive chemotherapy and surgical resection [10-14]. These inflammatory and nutritional status parameters are based on serum and/or blood counts in the peripheral blood and are routinely measured in daily clinical practice. Several studies have demonstrated an association between undernourishment based on low body mass index (BMI) and poor outcomes after allogeneic HCT in adults [15-18]. However, it would be difficult to conclude from BMI that nutritional status affects post-transplantation outcomes after CBT in adult patients, given that CBT might be advantageous in relatively smaller and lighter adults. Thus, we retrospectively evaluated the impact of pretransplantation inflammatory and nutritional status on post-transplantation outcomes in adult patients after a single CBT.

METHODS

Patient Selection

In our institution, unrelated cord blood is an alternative first-line donor source for patients without an HLA-matched sibling donor, unless the patient has anti-HLA antibodies against donor-specific antigens. Between March 2004 and July 2018, we performed single-unit CBT as the first allogeneic HCT for 207 adult patients at The Institute of Medical Science at The University of Tokyo. To clarify the prognostic impact of inflammatory and nutritional status immediately before initiation of the conditioning regimen on transplantation outcomes after a myeloablative single CBT, 37 patients were excluded from this study owing to a lack of laboratory data on inflammatory and nutritional

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status. Five patients received reduced-intensity conditioning based on the criteria of the Center for International Blood and Marrow Transplant Research [19]. The remaining 165 patients were included in the present analysis. All cord blood units were obtained from the Japan Cord Blood Bank Network, and the preferred cord blood unit was selected as reported previously [4,5]. This retrospective study was approved by the Institutional Review Board of The Institute of Medical Science at The University of Tokyo (30-38-B0824).

Inflammatory and Nutritional Status

To evaluate pretransplantation inflammatory and nutritional status, blood samples were obtained within 8 days before initiation of the conditioning regimen. The CONUT score was calculated based on the serum albumin concentration, total lymphocyte count (TLC), and total cholesterol, as described previously [20]. The PNI was calculated as 10 × serum albumin + .005 × TLC [21]. The GPS was scored based on from CRP and serum albumin levels [10]. The CAR was calculated by dividing the serum CRP level by the serum albumin level [14]. BMI was calculated by dividing the body weight in kilograms by the square of the height in meters. Median values of the CONUT score, PNI, CAR, and BMI served as cutoff values. GPS was divided into 2 groups: score of 0 and score of 1 or 2. All patients were classified into 2 groups based on these cutoff values for further analysis.

Definitions

Overall survival (OS; inverse of overall mortality) was defined as the time from the date of CBT to the date of death or last contact. Nonrelapse mortality (NRM) was defined as death during remission. Relapse was defined as morphologic evidence of disease. Neutrophil engraftment was defined as occurring on the first of 3 consecutive days of an absolute neutrophil count $>.5 \times 10^9$/L. Platelet engraftment was defined as occurring on the first of 7 consecutive days of a platelet count $>50 \times 10^9$/L from the last platelet transfusion. Acute and chronic graft-versus-host disease (GVHD) were graded according to standard criteria [22,23]. Early infection was defined as the development of bacterial or fungal infection within 100 days after CBT. The number of HLA disparities was defined as a low resolution for HLA-A, -B, and -DR. Disease status at the time of CBT was assessed according to the refined Disease Risk Index (DRI) [24].

Statistical Analysis

The probability of OS was estimated using the Kaplan-Meier method, and the groups were compared using the log-rank test. The probabilities of NRM, relapse, engraftment, GVHD, and early infection were estimated as cumulative incidences, considering competing risks, and the groups were compared using the Gray test. The Cox proportional hazards regression model for overall mortality or a Fine and Gray proportional hazards model for NRM, relapse, engraftment, GVHD, and early infection was used to estimate hazard ratios with 95% confidence interval (CI) in multivariate analysis. The following variables were considered in multivariate analysis: age (continuous), cytomegalovirus serostatus (negative versus positive), DRI (low/intermediate versus high/very high), cryopreserved cord blood total nucleated cell (TNC) count ($<2.5 \times 10^7$/kg versus $\geq 2.5 \times 10^7$/kg), cryopreserved cord blood CD34$^+$ cell count ($<1.0 \times 10^5$/kg versus $\geq 1.0 \times 10^5$/kg), HLA disparities (≤1 versus ≥2), sex incompatibility (female donor to male recipient versus others), and inflammatory and nutritional status, such as the CONUT score (<4 versus ≥4), PNI (≥43 versus <43), GPS (0 versus 1/2), CAR (<.04 versus ≥.04), and BMI (≥20.7 versus <20.7). All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [25], a graphical user interface for the R 3.3.2 software program (R Foundation for Statistical Computing, Vienna, Austria). All P values were 2-sided, and $P<.05$ was considered statistically significant.

Table 1
Patients and Cord Blood Transplantation Characteristics

Characteristic	Value
Number of patients	165
Age, yr, median (range)	44 (16-68)
Body weight, kg, median (range)	57.4 (38.4-104.0)
BMI, kg/m^2, median (range)	20.7 (14.2-33.5)
Sex, n (%)	
Male	101 (61)
Female	64 (39)
Recipient CMV serostatus, n (%)	
Positive	145 (88)
Negative	20 (12)
Disease type, n (%)	
Acute myelogenous leukemia	85 (52)
Acute lymphoblastic leukemia	35 (21)
Myelodysplastic syndrome	21 (13)
Chronic myelogenous leukemia/myeloproliferative neoplasm	9 (5)
Non-Hodgkin lymphoma/ adult T cell leukemia-lymphoma	11 (7)
Severe aplastic anemia	2 (1)
Chronic active Epstein-Barr virus infection	2 (1)
DRI, n (%)	
Low/intermediate	94 (57)
High/very high	66 (40)
Not available	5 (3)
Cryopreserved TNCs, $\times 10^7$/kg, median (range)	2.53 (1.32-5.69)
Cryopreserved CD34$^+$ cells, $\times 10^5$/kg, median (range)	.94 (.28-2.84)
HLA disparity, n (%)	
0	5 (3)
1	31 (19)
2	123 (75)
3	6 (4)
Sex incompatibility, n (%)	
Female donor to male recipient	49 (30)
Others	116 (70)

CMV indicates cytomegalovirus.

RESULTS

Characteristics of Patients and Inflammatory and Nutritional Status

The characteristics of patients and CBTs are summarized in Table 1. The median patient age was 44 years (range, 16 to 68 years), median weight was 57.4 kg (range, 38.4 to 104.0 kg), and median BMI was 20.7 kg/m^2 (range, 14.2 to 33.5 kg/m^2). The most common disease type was acute myelogenous leukemia (52%). The median TNC dose was 2.53 $\times 10^7$/kg (range, 1.32 to 5.69 $\times 10^7$/kg), and the median CD34$^+$ cell dose was .94 $\times 10^5$/kg (range, .28 to 2.84 $\times 10^5$/kg). The median follow-up period for survivors after CBT was 83 months (range, 2 to 175 months).

Blood samples were obtained at a median of 10 days (range, 8 to 16 days) before CBT and 2 days (range, 0 to 8 days) before initiation of the conditioning regimen. The median albumin, total cholesterol, CRP, and TLC values were as follows: albumin, 4.0 g/dL (range, 2.0 to 4.7 g/dL); total cholesterol, 166 mg/dL (range, 87 to 281 mg/dL); CRP, .16 mg/dL (range, .01 to 18.96 mg/dL); and TLC, .625 $\times 10^9$/L (range, .057 to 1.935 $\times 10^9$/L. The median CONUT score was 4 (range, 0 to 11), median PNI was 43 (range, 23 to 50), and median CAR was .04 (range, 0 to 9.48). The GPS was 0 in 138 patients (84%), 1 in 19 patients (12%), and 2 in 8 patients (5%). The higher CONUT score group, the lower PNI group, the GPS 1/2 group, and the higher CAR group, indicative of poor inflammatory and nutritional status, were significantly associated with one another, and each was significantly associated with the higher DRI group (Supplementary Table 1). There were no significant differences between the lower BMI group and the higher CONUT score group, the high GPS group, or the higher CAR group (Supplementary Table 1). Among 73 assessable patients with hematologic complete remission at CBT, inflammatory and nutritional status were not associated with minimal residual disease (MRD) status at CBT (Supplementary Table 1). The median CRP level was .09 mg/dL (range, .01 to .70 mg/dL) in patients without MRD and .11 mg/dL (range, .03 to .97 mg/dL) in patients with MRD (P = .602, Mann-Whitney U test) among patients with hematologic complete remission at CBT.

Survival, NRM, and Relapse

Among the entire cohort, the probability of OS at 5 years was 68% (95% CI, 59% to 75%). In univariate analysis by the log-rank test, GPS 0 and lower CAR were significantly associated with better OS, but lower BMI was not (Figure 1C-E). A trend toward better OS was observed in the lower CONUT score and higher PNI groups (Figure 1A and B). In multivariate analysis,

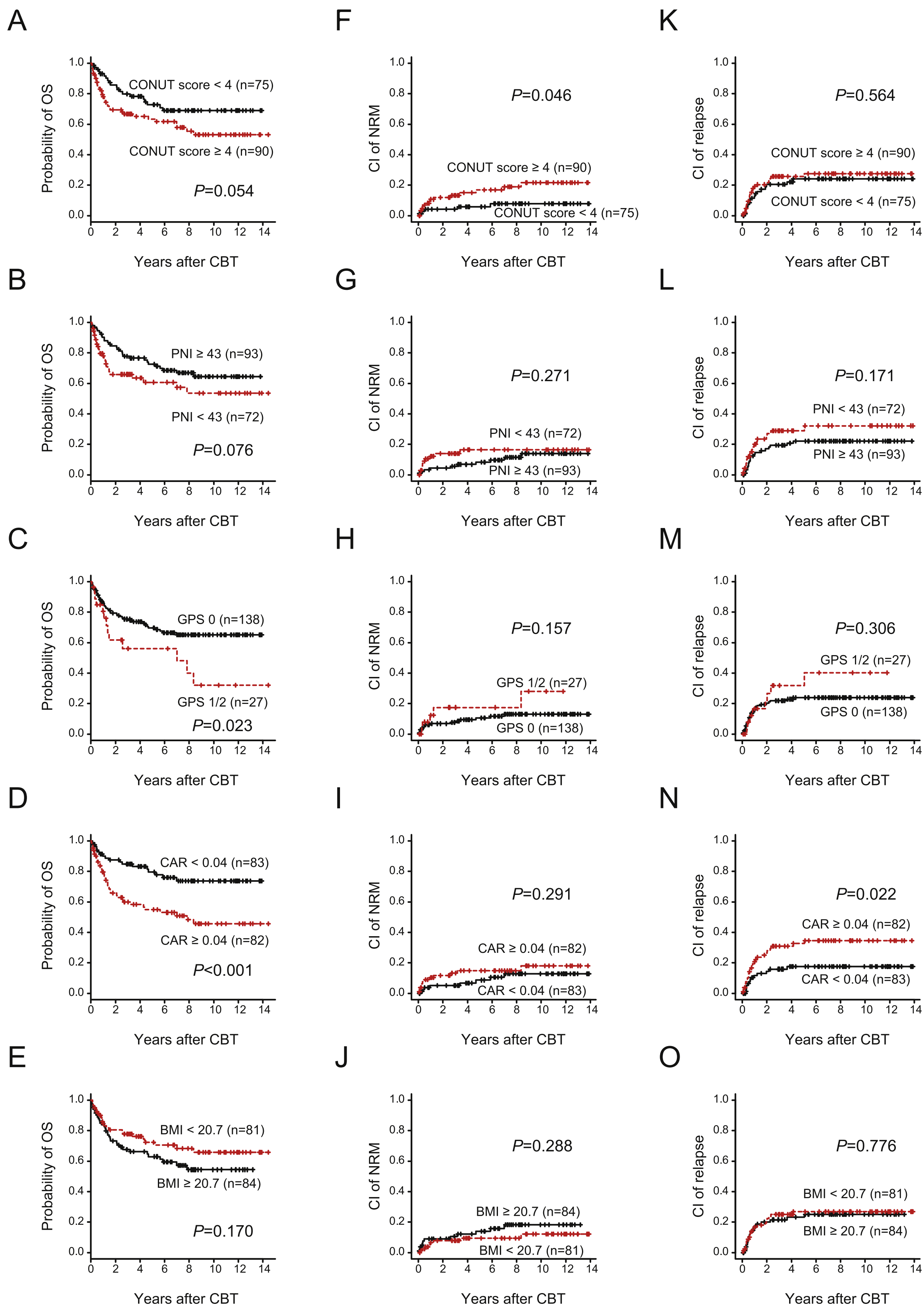

Figure 1. Probability of OS and cumulative incidences of NRM and relapse following single-unit cord blood transplantation according to CONUT score (A, F, and K), PNI (B, G, and L), GPS (C, H, and M), CAR (D, I, and N), and BMI (E, J, and O).

Table 2
Multivariate Analysis of Overall Mortality According to the CONUT score, PNI, GPS, CAR, and BMI

Variable	CONUT		PNI		GPS		CAR		BMI	
	HR (95% CI)	*P* Value	HR (95%CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.02 (.99-1.04)	.130	1.01 (.99-1.04)	.213	1.02 (.99-1.04)	.133	1.02 (.99-1.05)	.075	1.01 (.99-1.04)	.152
CMV-positive status	2.90 (.86-9.72)	.083	2.75 (.82-9.15)	.099	2.67 (.79-8.97)	.110	2.95 (.88-9.84)	.077	3.02 (.90-10.14)	.073
DRI high/very high	1.96 (1.11-3.47)	**.019**	2.07 (1.18-3.63)	**.010**	1.99 (1.12-3.53)	**.017**	1.81 (1.03-3.21)	**.039**	2.27 (1.28-4.01)	**.004**
TNCs $\geq 2.5 \times 10^7$/kg	.81 (.46-1.44)	.488	.80 (.45-1.41)	.449	.79 (.45-1.40)	.431	.79 (.45-1.41)	.442	.89 (.49-1.60)	.711
$CD34^+$ cells $\geq 1.0 \times 10^5$/kg	.78 (.42-1.45)	.435	.80 (.43-1.48)	.494	.78 (.42-1.45)	.445	.67 (.36-1.23)	.200	.79 (.43-1.45)	.459
HLA disparities ≥2	1.90 (.87-4.17)	.106	2.05 (.93-4.51)	.075	1.93 (.88-4.23)	.099	1.83 (.82-4.06)	.134	1.87 (.85-4.11)	.114
Sex incompatibility, F to M	1.27 (.69-2.33)	.426	1.32 (.72-2.40)	.358	1.23 (.67-2.27)	.494	1.28 (.71-2.31)	.406	1.14 (.61-2.14)	.666
CONUT ≥4	1.52 (.86-2.68)	.146								
PNI <43			1.43 (.81-2.52)	.209						
GPS 1/2					1.61 (.84-3.09)	.149				
CAR ≥.04							2.42 (1.35-4.36)	**.002**		
BMI <20.7									.67 (.36-1.24)	.206

F to M indicates female donor to male recipient; HR, hazard ratio.
The *P* values in bold are statistically significant (<.05).

higher CAR alone was significantly associated with higher overall mortality (Table 2).

The cumulative incidences of NRM and relapse at 5 years were 12% (95% CI, 7% to 18%) and 25% (95% CI, 18% to 32%), respectively. Higher CONUT score alone was significantly associated with higher NRM in univariate analysis (Figure 1F-J). In multivariate analysis, a trend toward a higher incidence of NRM was observed in the higher CONUT score group (Supplementary Table 2). In univariate analysis performed using the Gray test, higher CAR alone was significantly associated with a higher incidence of relapse (Figure 1K-O). In multivariate analysis, a trend toward higher incidence of relapse was observed in the lower PNI score group (Supplementary Table 3).

Neutrophil and Platelet Engraftment

Among the entire cohort, the cumulative incidence of neutrophil engraftment was 97% (95% CI, 91% to 99%) at day 42 after CBT, with a median time to achieving neutrophil engraftment $>.5 \times 10^9$/L of 21 days (range, 15 to 50 days). In univariate analysis, lower CONUT score and higher PNI were significantly associated with achievement of neutrophil engraftment (Figure 2A-E). In multivariate analysis, higher CONUT score and higher CAR were significant negative predictive factors for achievement of neutrophil recovery (Table 3).

The cumulative incidence of platelet engraftment was 90% (95% CI, 83% to 94%) at day 100 after CBT, with median time to an untransfused platelet count $>50 \times 10^9$/L of 45 days (range, 27 to 302 days). In univariate analysis, lower CONUT score and higher PNI were significantly associated with achievement of platelet engraftment (Figure 2F-J). In multivariate analysis, inflammatory and nutritional status were not associated with achievement of platelet engraftment, but a trend toward lower incidence of platelet engraftment was observed in the lower PNI group (Supplementary Table 4).

GVHD and Early Infection

Among the entire cohort, the cumulative incidence of grade III−IV acute GVHD was 13% (95% CI, 8% to 18%) at 100 days. In univariate analysis, higher CONUT score and lower PNI were significantly associated with the development of grade III-IV acute GVHD (Figure 3A-E). In multivariate analysis, inflammatory and nutritional status were not associated with the development of grade III-IV acute GVHD (Supplementary Table 5).

The cumulative incidence of extensive chronic GVHD was 26% (95% CI, 19% to 34%) at 3 years after CBT. In univariate analysis, a trend toward a higher incidence of extensive chronic GVHD was observed in the higher CONUT score group (Figure 3F-J). In multivariate analysis, higher CONUT score alone was significantly associated with the development of extensive chronic GVHD (Supplementary Table 6).

The cumulative incidence of early infection was 21% (95% CI, 15% to 27%) at day 100 after CBT. In univariate analysis, inflammatory and nutritional status were not associated with the development of early infection after CBT (Supplementary Figure 1). In multivariate analysis, higher PNI was a significant predictive factor for the development of early infection after CBT (Supplementary Table 7).

DISCUSSION

The purpose of this single-center retrospective study was to evaluate the impact of pretransplantation inflammatory and nutritional status on post-transplantation outcomes in adult recipients of myeloablative single CBT. Several previous studies in which malnutrition was evaluated by BMI [15-18] or the Scored Patient Generated-Subjective Global Assessment questionnaire [26] have shown that pretransplantation malnutrition is associated with poor survival after allogeneic HCT. In the present study, pretransplantation inflammatory and nutritional status, as assessed by CONUT score, PNI, GPS, and CAR, significantly affected hematopoietic engraftment, severe GVHD, NRM, and survival in adults after a single CBT, but BMI did not. Further, the higher CONUT score group, the lower PNI group, the higher GPS group, and the higher CAR group were associated with one another, but CONUT score, GPS, and CAR were not correlated with BMI. BMI may be not a sensitive indicator of nutritional status, because some patients with malnutrition have ascites or edema. Therefore, compared with BMI, pretransplantation inflammatory and nutritional status as assessed by CONUT score, PNI, GPS, and CAR are better predictors of transplantation outcomes after single CBT.

We previously identified $CD34^+$ cell dose based on actual body weight as the best predictor of hematopoietic recovery after a single CBT [27]. Relatively smaller and lighter adults might receive more therapeutic benefit from a single CBT. Although Paviglianiti et al [28] reported that BMI was not associated with neutrophil engraftment after CBT in children and young adults with acute leukemia, the impact of BMI on hematopoietic engraftment after CBT in adult patients is unclear. In the present study, although multivariate analysis demonstrated that $CD34^+$ cell dose based on actual body weight was found to be the best predictor of neutrophil and platelet engraftment, CONUT score and CAR, but not BMI, were also independently associated with successful achievement of neutrophil engraftment after CBT. Therefore, apart from cell

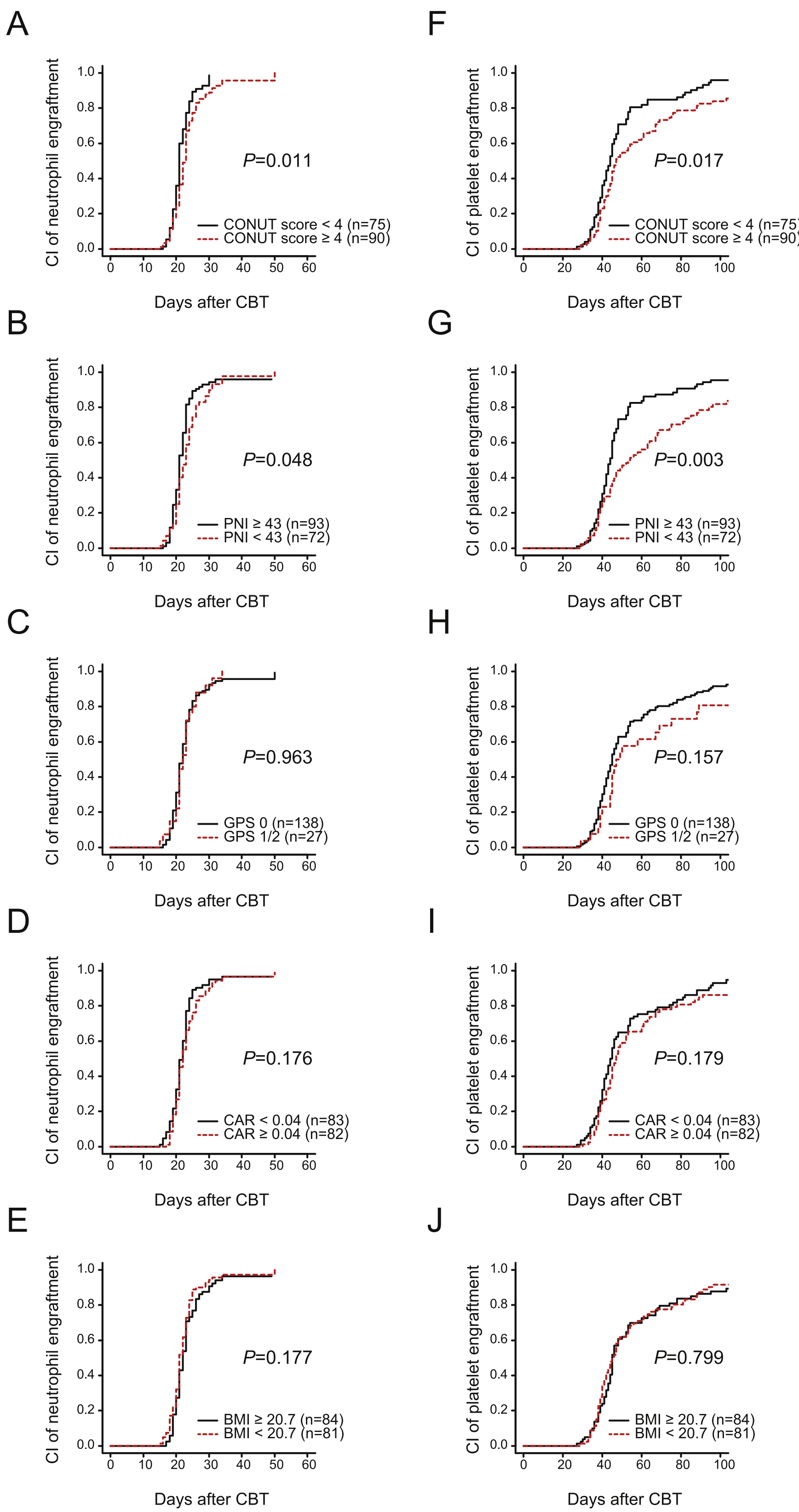

Figure 2. Cumulative incidences of neutrophil and platelet engraftment following single-unit cord blood transplantation according to CONUT score (A and F), PNI (B and G), GPS (C and H), CAR (D and I), and BMI (E and J).

Table 3
Multivariate Analysis of Neutrophil Engraftment According to CONUT score, PNI, GPS, CAR, and BMI

Variable	CONUT		PNI		GPS		CAR		BMI	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	.98 (.97-.99)	**.045**	.98 (.97-1.00)	.084	.98 (.97-.99)	**.029**	.98 (.97-.99)	**.027**	.98 (.97-.99)	**.028**
CMV-positive status	.86 (.52-1.42)	.570	.90 (.53-1.52)	.700	.86 (.51-1.45)	.580	.85 (.51-1.43)	.550	.85 (.52-1.39)	.540
DRI high/very high	.88 (.64-1.19)	.420	.85 (.62-1.15)	.300	.80 (.58-1.12)	.200	.90 (.67-1.21)	.520	.80 (.59-1.09)	.170
TNC $\geq 2.5 \times 10^7$/kg	1.05 (.78-1.39)	.740	1.06 (.80-1.41)	.660	1.07 (.80-1.42)	.630	1.08 (.81-1.43)	.590	1.06 (.80-1.41)	.670
$CD34^+$ cells $\geq 1.0 \times 10^5$/kg	2.75 (2.03-3.74)	<**.001**	2.71 (1.99-3.69)	<**.001**	2.71 (1.98-3.69)	<**.001**	2.89 (2.12-3.94)	<**.001**	2.71 (1.99-3.69)	<**.001**
HLA disparities ≥2	.72 (.53-.99)	**.048**	.72 (.53-.98)	**.040**	.77 (.57-1.04)	.096	.75 (.55-1.02)	.067	.77 (.56-1.05)	.110
Sex incompatibility, F to M	.89 (.65-1.20)	.450	.86 (.64-1.16)	.340	.85 (.63-1.16)	.320	.89 (.66-1.21)	.470	.87 (.63-1.21)	.430
CONUT ≥4	.72 (.53-.98)	**.039**								
PNI <43			.81 (.58-1.11)	.200						
GPS 1/2					1.04 (.69-1.57)	.830				
CAR ≥.04							.68 (.50-.91)	**.009**		
BMI <20.7									1.07 (.79-1.45)	.640

The *P* values in bold are statistically significant (<.05).

dose based on actual body weight, malnutrition status may be an independent predictor for poor neutrophil recovery after single CBT.

Several recent studies have demonstrated that higher CONUT score and higher GPS score are significantly associated with higher NRM in adult recipients of allogeneic HCT [29,30]; however, the causative relationship between these variables was unclear in these studies. Serum albumin is a marker of nutritional status, as well as of systemic chronic inflammation. The CONUT score, PNI, GPS, and CAR all include serum albumin in their calculation. Several studies have shown that pretransplantation hypoalbuminemia is predictive of NRM after allogeneic HCT [31-33]. In the present study, higher CONUT score was associated with the development of grade III-IV acute GVHD in univariate analysis and with the development of extensive chronic GVHD in multivariate analysis, as well as with poor neutrophil recovery, which might have contributed to higher NRM after single CBT. In contrast, CRP is one of the most useful acute-phase proteins for assessing inflammation. GPS and CAR include CRP in the calculations. Several studies have demonstrated significant associations between higher pretransplantation CRP and higher NRM and poor OS in patients after allogeneic HCT [34-37]. In our study, initiation of the conditioning regimen is determined depending on the patient's condition, because stored cord blood units are available at the clinician's convenience, particularly in patients with remission at CBT. Therefore, the elective timing of CBT might have contributed to the lack of influence of pretransplantation CRP-based markers, such as GPS and CAR, on NRM in our study.

In this study, poor inflammatory and nutritional status, as demonstrated by higher CONUT score, lower PNI, higher GPS, and higher CAR, were significantly associated with higher DRI. Poor inflammatory and nutritional status in patients with higher DRI might be related to the presence of aggressive disease and treatment. In this study, higher CAR was correlated with a higher incidence of relapse in univariate analysis, but not in multivariate analysis. This is due in part to a strong correlation between poor inflammatory and nutritional status and higher DRI, which is the most powerful predictor of relapse. These data suggest that poor inflammatory and nutritional status do not affect the incidence of relapse after single CBT.

Our findings show that several markers of inflammatory and nutritional status are associated with the achievement of engraftment and development of severe GVHD. Although the exact mechanism underlying these associations remains unclear, a possible explanation for these findings is that poor inflammatory and nutritional status, such as hypoalbuminemia and elevated CRP level, might indicate the presence of latent infection and occult tissue injury before conditioning, which could contribute to the induction of a systemic inflammation response or organ failure due to the conditioning regimen and neutropenia. Finally, poor neutrophil engraftment and severe GVHD might be due in part to a systemic inflammation response or organ failure. However, we did not find an association between poor inflammatory and nutritional status and the development of early bacterial or fungal infection after CBT.

Our study clearly demonstrates that several markers of inflammatory and nutritional status are predictive of transplantation outcomes after myeloablative single CBT for adults. However, our study has several limitations. First, our study was a retrospective, single-institution analysis in Japan, and the number of patients was small. Further studies are needed to validate the correlation between these inflammatory and nutritional status indicators and transplantation outcomes in adult recipients of CBT. Second, the cutoff values of CONUT score, PNI, and CAR for prediction of transplantation outcomes were determined using median values, whereas different cutoff values were used in previous studies [11,12,14]. Although optimal cutoff values may vary according to the study population, further studies are needed to establish the best cutoff values in adult patients after allogeneic HCT. Third, nutritional intervention, such as the use of i.v. hyperalimentation in patients with reduced food intake, was part of daily clinical practice during the study period; however, we were unable to evaluate the effects of these interventions on inflammatory and nutritional status and transplantation outcomes in this study.

In conclusion, our data demonstrate that pretransplantation inflammatory and nutritional status indicators, such as the CONUT score, PNI, GPS, and CAR, may be practical and easily evaluable parameters for predicting outcomes after myeloablative single CBT, superior to BMI. Further studies are needed to confirm the relationship between these indicators of inflammatory and nutritional status and transplantation outcomes in adult patients after CBT.

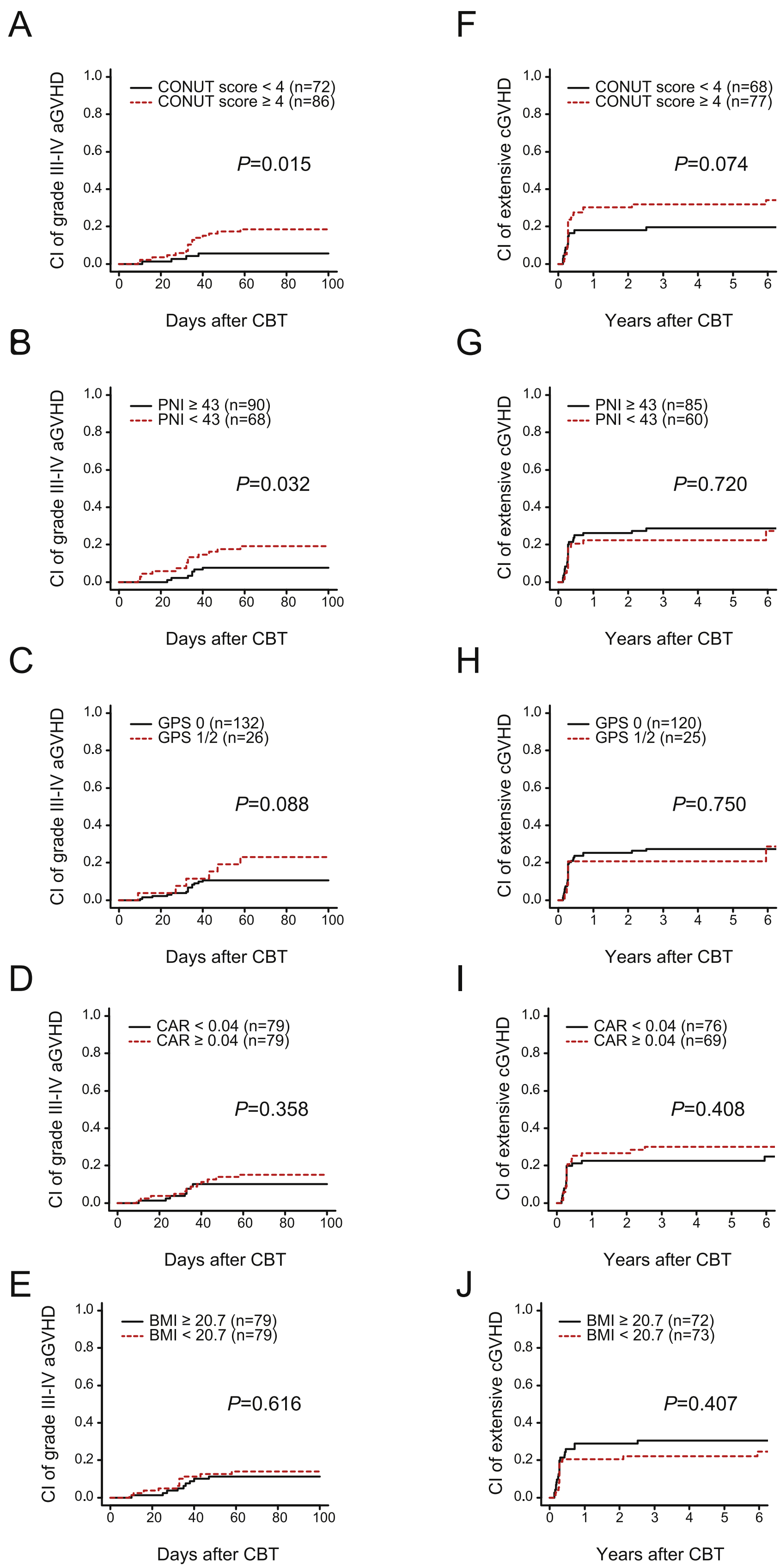

Figure 3. Cumulative incidences of grade III-IV acute GVHD and extensive chronic GVHD following single-unit cord blood transplantation according to CONUT score (A and F), PNI (B and G), GPS (C and H), CAR (D and I), and BMI (E and J).

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.01.006.

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