RESEARCH ARTICLE

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The Composite Health Risk Assessment Model (CHARM) Predicts Overall Mortality and Relapse, But Not Non-Relapse Mortality, in Adults Following Unrelated Single-Unit Cord Blood Transplantation

Bileşik Sağlık Riski Değerlendirme Modeli (CHARM), Akraba Dışı Tek Ünite Kordon Kanı Nakli Sonrası Yetişkinlerde Genel Ölüm Oranını ve Nüks Oranını Tahmin Eder, Ancak Nüks Olmayan Ölüm Oranını Tahmin Etmez

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Abstract

Objective: Concerns about excessive non-relapse mortality (NRM) are a major issue following allogeneic hematopoietic cell transplantation (HCT). Although the HCT-Specific Comorbidity Index (HCT-CI) was established as a stratification model for NRM following allogeneic HCT, the Composite Health Risk Assessment Model (CHARM) score was also developed to predict the risk of NRM and overall mortality following allogeneic HCT from adult donors, particularly in older patients. The CHARM score has been shown to predict these outcomes better than the HCT-CI alone. However, the prognostic value of the CHARM score has not been validated in adult patients undergoing unrelated single-unit cord blood transplantation (CBT). This study aimed to address that gap in the research.

Materials and Methods: We retrospectively validated the impact of the CHARM score on transplant outcomes in 321 adults who underwent unrelated single-unit CBT at our institution.

Results: In univariate analysis, a higher CHARM score was significantly associated with worse overall mortality (p<0.001), higher relapse (p=0.007), and NRM (p=0.048). In multivariate analysis, the rates of overall mortality (hazard ratio [HR]: 1.56, 95% confidence interval [CI]: 1.06-2.29, p=0.022) and relapse (HR: 1.71, 95% CI: 1.09-2.69, p=0.020) were significantly higher in patients with higher CHARM scores, but NRM was not (HR: 1.17, 95% CI: 0.68-1.99, p=0.560). The detrimental effects of higher CHARM scores on overall mortality and relapse compared to lower CHARM scores were observed in subgroups of patients with high and very high risk, as defined by the refined Disease Risk Index.

Öz

Amaç: Allojenik hematopoetik hücre nakli (HKH) sonrasında artmış nükssüz mortalite (NRM) ile ilgili endişeler önemli bir sorundur. HKH-Spesifik Komorbidite İndeksi (HCT-CI), allojenik HKH'ni takiben NRM için bir sınıflandırma modeli olarak belirlenmiş olsa da, özellikle yaşlı hastalarda, yetişkin donörlerden yapılan allojenik HKH'ni takiben NRM riskini ve genel mortaliteyi tahmin etmek için Bileşik Sağlık Risk Değerlendirme Modeli (CHARM) skoru da geliştirilmiştir. CHARM skorunun bu sonuçları tek başına HKH-CI'dan daha iyi öngördüğü gösterilmiştir. Ancak, CHARM skorunun prognostik değeri, akraba dışı tek ünite kordon kanı nakli (KKT) uygulanan yetişkin hastalarda doğrulanmamıştır. Bu çalışma, araştırmalarda bu boşluğu gidermeyi amaçlamaktadır.

Gereç ve Yöntemler: Kurumumuzda akraba dışı tek ünite KKT uygulanan 321 yetişkinde CHARM skorunun nakil sonuçları üzerindeki etkisini geriye dönük doğruladık.

Bulgular: Tek değişkenli analizde, daha yüksek CHARM skoru daha kötü genel mortalite (p<0,001), daha yüksek nüks (p=0,007) ve NRM (p=0,048) ile anlamlı şekilde ilişkiliydi. Çok değişkenli analizde, genel mortalite oranları (tehlike oranı [HR]: 1,56, %95 güven aralığı [GA]: 1,06-2,29, p=0,022) ve nüks (HR: 1,71, %95 GA: 1,09-2,69, p=0,020) daha yüksek CHARM skorlu hastalarda anlamlı şekilde daha yüksekti, ancak NRM değildi (HR: 1,17, %95 GA: 0,68-1,99, p=0,560). Geliştirilmiş Hastalık Riski İndeksi'ne göre yüksek ve çok yüksek riskli hasta alt gruplarında, daha düşük CHARM puanlarına kıyasla daha yüksek CHARM puanlarının genel mortalite ve nüks üzerindeki olumsuz etkileri gözlenmiştir.

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Abstract

Conclusion: In contrast to previous research, this study revealed that the CHARM score was able to predict overall mortality and relapse, but not NRM, in adults undergoing single-unit CBT.

Keywords: Cord blood transplantation, Composite Health Risk Assessment Model, Non-relapse mortality, HCT-Specific Comorbidity Index, Risk stratification, Allogeneic hematopoietic cell transplantation

Öz

Sonuç: Önceki araştırmaların aksine, bu çalışma CHARM puanının tek ünite CBT uygulanan yetişkinlerde genel mortalite ve nüksü öngörebildiğini, ancak NRM'yi öngöremediğini ortaya koymuştur.

Anahtar Sözcükler: Kordon kanı nakli, Bileşik Sağlık Riski Değerlendirme Modeli, Nüks dışı mortalite, HCT'ye Özgü Eşlik Eden Hastalık İndeksi, Risk sınıflandırması, Allojenik hematopoetik hücre nakli

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a possibly curative intervention for refractory hematopoietic disorders. Nonetheless, apprehensions persist regarding elevated non-relapse mortality (NRM) as a substantial problem in allogeneic HCT. Several prognostic models, such as the HCT-Specific Comorbidity Index (HCT-CI) [1], the Pretransplantation Assessment of Mortality (PAM) score [2,3], the European Society for Blood and Marrow Transplantation risk score [4], the NRM-J index [5], and the Treatment-Related Mortality (TRM) score [6], have been developed to predict NRM following allogeneic HCT. Among these, the HCT-CI has set a global standard for estimating NRM risk and guiding treatment decisions before HCT [7,8]. Recently, the Composite Health Risk Assessment Model (CHARM) was developed to improve the risk stratification of 1-year NRM and overall mortality following allogeneic HCT in older patients, as demonstrated in the prospective BMT CTN 1704 study [9]. The CHARM score was found to be more effective than the HCT-CI alone in this context [9].

Cord blood transplantation (CBT) serves as a recognized alternative to allogeneic HCT [10,11,12,13]. Delayed hematological recovery and an elevated risk of infectious complications are recognized disadvantages of CBT, resulting in an increased risk of NRM [14]. Despite this, several studies have shown that the HCT-CI fails to predict NRM [15,16] or overall survival (OS) [16,17] in CBT recipients. However, the HCT-CI was validated in a large cohort of CBT recipients in our previous research [18]. Attempts to validate the HCT-CI in the setting of CBT have yielded mixed results. Nonetheless, the prognostic significance of the original CHARM score remains unexplored in adults receiving unrelated single-unit CBT. To address this gap, we conducted a retrospective analysis to assess whether the CHARM score influences posttransplant outcomes in adults who underwent CBT at our institution.

Materials and Methods

Study Design and Participants

This was a retrospective study conducted at a single center in Japan. The analysis entailed a retrospective review of adult patients who underwent single-unit CBT at the Institute of Medical Science, the University of Tokyo from August 1998 to December 2023. Clinical data were acquired retrospectively from medical records. During the period in question, we conducted single-unit CBT as the initial allogeneic HCT process for 341 adult patients at our hospital. Nineteen patients unable to be assessed for the HCT-CI and one patient unable to be evaluated for alterations in body weight were eliminated from the retrospective analysis as their CHARM scores could not be computed. A total of 321 patients were ultimately included in the study. All cord blood units were sourced from the Cord Blood Bank of Japan.

The conditioning regimen and graft-versus-host disease (GVHD) prevention protocol were established by the patients' physicians according to the characteristics of the patient and the disease [19,20,21], and the majority of patients received comparable supportive care [22] and transfusion delivery [23]. This retrospective study was performed in compliance with the Declaration of Helsinki. The Institutional Review Board of the University of Tokyo's Institute of Science approved this retrospective study (decision no: 2024-32-0823, date: September 2, 2024) and the implementation of an opt-out consent system.

Study Endpoints

The primary endpoint was the effect of the CHARM score on OS after CBT. The secondary endpoints included the influence of the CHARM score on relapse, NRM, hematological recovery, and both acute and chronic GVHD following CBT.

Definitions

The CHARM score was retrospectively computed using the following formula: 0.15310 x (HCT-CI) + 0.13247 x (LOG(CRP)) - 0.71227 x (albumin) + 0.00119 x (% weight)^2, derived from medical records as per the original report [9]. Serum C-reactive protein (CRP) and albumin levels were measured within 3 days preceding the beginning of the conditioning regimen.

Neutrophil and platelet recovery were defined as an absolute neutrophil count surpassing 0.5x10^9/L and a platelet count above 20x10^9/L without the necessity of platelet transfusions on the first day of 3 and 7 consecutive days, respectively. The diagnosis and severity of acute and chronic GVHD were assessed according to published standard criteria [24,25].

OS was defined as the interval between the date of CBT and the date of death or the most recent follow-up. Relapse was characterized by morphological indications of hematological disease. NRM was characterized as mortality occurring during remission. The HCT-CI [1] and the refined Disease Risk Index (DRI) [26] were categorized based on established criteria. The number of human leukocyte antigen (HLA) discrepancies was ascertained using low-resolution typing for HLA-A, HLA-B, and HLA-DR in the graft-versus-host direction.

Statistical Analysis

Comparisons of baseline characteristics between two CHARM score groups (lower versus higher) were conducted using the Mann-Whitney U test for continuous variables and the chi-square or Fisher exact test for categorical variables. The analysis of hematopoietic recovery, GVHD, relapse, and NRM between the two CHARM score groups was conducted using the cumulative incidence method, which takes into account competing risks, and Gray's test. The Kaplan-Meier method and log-rank test were employed to analyze the difference in OS between the two CHARM score groups.

The Fine-Gray proportional hazards model was employed in multivariate analysis to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for hematopoietic recovery, GVHD, relapse, and NRM, whereas the Cox proportional hazards regression model was applied for OS. The adjusted HRs and 95% CIs for the CHARM score (lower versus higher) were calculated, accounting for all covariates, including age at the time of CBT (<45 years versus ≥45 years), recipient's sex (male versus female), refined DRI score (low/intermediate versus high/very high), conditioning regimen (total body irradiation [TBI] of 10-12 Gy versus TBI of 2-4 Gy), cryopreserved cord blood total nucleated cell count (<2.5x10^7/kg versus ≥2.5x10^7/kg), and HLA disparities (0 or 1 versus 2 or 3).

EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), was used for statistical analyses [27]. Statistically significant p values were less than 0.05 as determined using a two-sided test.

Results

Patient Characteristics

Among the entire cohort, the median CHARM score was -3.31 (range: -7.45 to 3.81). To assess the impact of the CHARM score on posttransplant outcomes, patients were categorized into three groups based on similar cut-off values from the original report [9] (<-2.50149 versus -2.50149 to -2.01456 versus ≥-2.01456) (Supplementary Figure 1). Based on these data, for further univariate and multivariate analyses, the patients were divided into two groups according to the original report [9] (lower group: values less than -2.01; higher group: values greater than or equal to -2.01). The lower CHARM score group consisted of 223 patients (69.5%) and the higher CHARM score group included 98 patients (30.5%). The patient and CBT characteristics of the two CHARM score groups are shown in Table 1. The median follow-up for survivors in the total group was 121 months, ranging from 4 to 287 months.

Patients with higher CHARM scores were older and more likely to have a high or very high refined DRI score compared to those with lower CHARM scores. In contrast, patients with lower CHARM scores were more likely to receive TBI-based myeloablative conditioning regimens and GVHD prophylaxis based on cyclosporine and methotrexate. Disease types varied between the two CHARM score groups. The median follow-up for survivors was 120 months (range: 4-273 months) in the group with lower CHARM scores and 103 months (range: 9-287 months) in the group with higher CHARM scores (p=0.315) (Table 1).

Neutrophil and Platelet Recovery

In univariate analysis, the cumulative incidence of neutrophil recovery was comparable between the two CHARM score groups (90.7% for the lower group and 87.6% for the higher group at 30 days, p=0.162) (Supplementary Figure 2A). The cumulative incidence of platelet recovery was also similar between the two groups (83.1% for the lower group and 77.6% for the higher group at 60 days, p=0.069) (Supplementary Figure 2B). In multivariate analysis, the CHARM score was not associated with neutrophil recovery (HR: 0.88, 95% CI: 0.69-1.12, p=0.320) or platelet recovery (HR: 0.82, 95% CI: 0.64-1.04, p=0.110) (Supplementary Table 1).

GVHD

In univariate analysis, the cumulative incidence of grades II to IV acute GVHD (p=0.253) and grades III to IV acute GVHD (p=0.640) was similar between the two CHARM score groups (Supplementary Figures 3A and 3B). In multivariate analysis, the CHARM score was not associated with grades II to IV acute GVHD (HR: 0.75, 95% CI: 0.54-1.04, p=0.091) or grades III to IV acute GVHD (HR: 0.76, 95% CI: 0.36-1.58, p=0.470) (Supplementary Table 2).

In univariate analysis, the cumulative incidence of extensive chronic GVHD was also similar between the two CHARM score groups (p=0.235) (Supplementary Figure 3C). In multivariate analysis, the CHARM score was not associated with extensive chronic GVHD (HR: 0.73, 95% CI: 0.42-1.28, p=0.280) (Supplementary Table 2).

OS, Relapse, and NRM

In univariate analysis, OS was significantly worse in the higher CHARM score group compared to the lower CHARM score group

(65.4% for the higher group and 79.1% for the lower group at 2 years, p<0.001) (Figure 1A). In multivariate analysis, a higher CHARM score was significantly associated with increased overall mortality (HR: 1.56, 95% CI: 1.06-2.29, p=0.022) (Table 2).

In univariate analysis, the cumulative incidence of relapse was significantly worse in the higher CHARM score group compared to the lower CHARM score group (29.5% for the higher group and 18.2% for the lower group at 2 years, p=0.007) (Figure 1B). In multivariate analysis, a higher CHARM score was significantly associated with higher relapse rates (HR: 1.71, 95% CI: 1.09-2.69, p=0.020) (Table 2).

In univariate analysis, the cumulative incidence of NRM was significantly worse in the group with higher CHARM scores compared to the group with lower CHARM scores (15.5% for the higher group and 9.1% for the lower group at 2 years, p=0.048) (Figure 1C). In multivariate analysis, the CHARM score was not associated with NRM (HR: 1.17, 95% CI: 0.68-1.99, p=0.560) (Table 2).

Subgroup Analysis According to Disease Type, Disease Risk, and Conditioning Regimen

Because disease type, disease status, or conditioning regimen could affect the posttransplant outcomes in adults who have undergone CBT, we also analyzed the effects of CHARM score stratification according to disease type (acute myeloid leukemia/myelodysplastic syndrome [AML/MDS] or acute lymphoblastic leukemia/non-Hodgkin's lymphoma [ALL/NHL]), refined DRI score (low/intermediate or high/very high), and conditioning regimen (TBI of 12 Gy).

In univariate analysis, the beneficial effects of lower CHARM scores on OS compared to higher CHARM scores were observed in the subgroups of patients with AML/MDS (78.6% versus 64.8% at 2 years, p=0.002), high and very high risk according to the refined DRI (68.8% versus 52.1% at 2 years, p<0.001), and TBI conditioning regimens based on 12 Gy (80.1% versus 68.7% at 2 years, p=0.011), but not in the subgroups of patients with ALL/NHL or low and intermediate risk according to the refined DRI (Figures 2A, 3A, and 4A).

In univariate analysis, the beneficial effects of lower CHARM scores on relapse compared to higher CHARM scores were also observed in the subgroups of patients with AML/MDS (17.8% versus 28.4% at 2 years, p=0.022), high and very high risk according to the refined DRI (28.5% versus 40.4% at 2 years, p=0.045), and TBI conditioning regimens based on 12 Gy (18.9% versus 27.0% at 2 years, p=0.040), but not in the subgroups of patients with ALL/NHL or low and intermediate risk according to the refined DRI (Figures 2B, 3B, and 4B). The cumulative incidence of NRM was comparable between the two CHARM score groups irrespective of disease type, disease risk, or TBI conditioning regimen based on 12 Gy (Figures 2C, 3C, and 4C). When restricted to patients who received TBI conditioning regimens based on 12 Gy, the CHARM score was not associated with the incidence of acute or chronic GVHD in univariate analysis (Figures 4D, 4E, and 4F).

Impact of Serum CRP and Albumin Levels on Relapse and NRM

We further evaluated whether serum CRP and albumin levels affected relapse and NRM. When patients were divided into two groups according to approximate median values of serum CRP (<0.15 mg/dL versus ≥0.15 mg/dL) and albumin

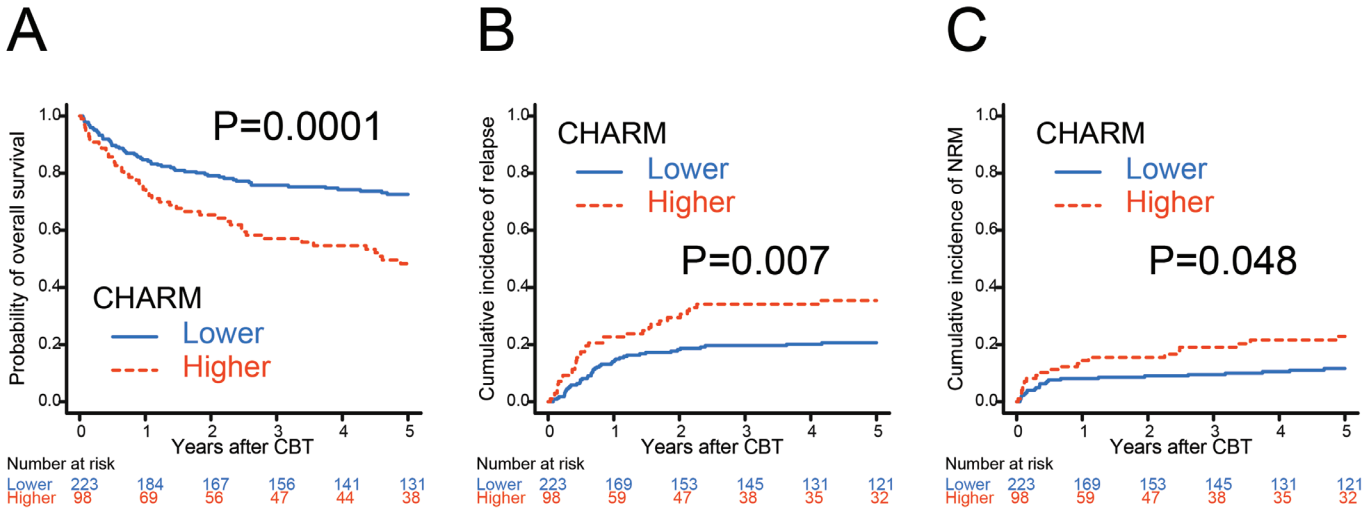

Figure 1. Unadjusted probability of overall survival (A) and cumulative incidences of relapse (B) and non-relapse mortality (C) following single-unit cord blood transplantation, stratified by the Composite Health Risk Assessment Model score.

CBT: Cord blood transplantation; CHARM: Composite Health Risk Assessment Model.

Table 1. Characteristics of patients and transplantations.

CHARM	Lower (less than -2.01)	Higher (greater than or equal to -2.01)	p
Number of CBTs	223 (69.5)	98 (30.5)	
Age, years, median (IQR)	43 (32.5-55.0)	48.5 (38.3-58)	**<0.001**
Sex			
Male	130 (58.3)	75 (56.0)	0.266
Female	34 (29.3)	59 (44.0)	
HCT-CI score			
0-2	202 (90.6)	82 (83.7)	0.088
≥3	21 (9.4)	16 (16.3)	
Diagnosis			
AML	109 (48.9)	61 (62.2)	**0.036**
ALL	55 (24.7)	9 (9.2)	
MDS	29 (13.0)	14 (14.3)	
CML	10 (4.5)	3 (3.1)	
MPD, PMF, CMML	5 (2.2)	4 (4.1)	
CAEBV	1 (0.4)	3 (3.1)	
NHL	11 (4.9)	3 (3.1)	
Mastocytosis	1 (0.4)	0 (0.0)	
SAA	2 (0.9)	1 (1.0)	
Refined Disease Risk Index			
Low/intermediate/undetermined	129 (59.2)	34 (37.0)	**<0.001**
High/very high	89 (40.8)	58 (63.0)	
Conditioning regimen			
TBI12Gy+HDAC+G+CY	113 (50.7)	56 (57.1)	**<0.001**
TBI12Gy+HDAC+CY	52 (23.3)	7 (7.1)	
TBI12Gy+CY	16 (7.2)	5 (5.1)	
TBI12Gy+HDAC+G+Flu	7 (3.1)	0 (0.0)	
TBI10Gy+HDAC+G+CY	10 (4.5)	0 (0.0)	
TBI4Gy+Flu+Bu3+HDAC	24 (10.8)	20 (20.4)	
TBI2Gy+HDAC+G+Flu	1 (0.4)	5 (5.1)	
TBI4Gy+Flu+Mel	0 (0.0)	5 (5.1)	
GVHD prophylaxis			
CSP+MTX	195 (87.4)	67 (68.4)	**<0.001**
CSP+MMF, CSP only	28 (12.4)	31 (31.6)	
Cryopreserved TNC dose (IQR), x10^7/kg	2.52 (2.16-3.10)	2.53 (2.15-2.98)	0.606
Cryopreserved CD34+ cell dose (IQR), x10^5/kg	1.00 (0.72-1.28)	0.95 (0.71-1.29)	0.387
Cryopreserved CFU-GM dose (IQR), x10^3/kg	29.16 (20.67-41.51)	26.51 (20.55-38.05)	0.588
HLA disparities*			
0-1	71 (31.8)	34 (34.7)	0.608
2	152 (68.2)	64 (65.3)	
Follow-up for survivors, months, median (range)	120 (4-273)	103 (9-287)	0.315

CHARM: Composite Health Risk Assessment Model; CBT: cord blood transplantation; IQR: interquartile range; HCT-CI: Hematopoietic Cell Transplantation-Specific Comorbidity Index; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; CML: chronic myelogenous leukemia; CMML: chronic myelomonocytic leukemia; CAEBV: chronic active Epstein-Barr virus infection; MPN: myeloproliferative neoplasm; ATL: adult T-cell leukemia; NHL: non-Hodgkin's lymphoma; MM: multiple myeloma; SAA: severe aplastic anemia; TBI: total body irradiation; Flu: fludarabine; Bu: busulfan; HDAC: high-dose cytarabine; Mel: melphalan; GVHD: graft-versus-host disease; CSP: cyclosporine; MTX: methotrexate; MMF: mycophenolate mofetil; TNC: total nucleated cell; CFU-GM: colony-forming unit granulocyte-macrophage; HLA: human leukocyte antigen; CY: cyclophosphamide; G: granulocyte-colony stimulating factor.

*: The number of HLA disparities was defined as a low resolution for HLA-A, HLA-B, and HLA-DR in the graft-versus-host direction. The p values in bold are statistically significant (p<0.05).

(<3.9 g/dL versus ≥3.9 g/dL), the cumulative incidence of relapse was significantly worse in the group with higher CRP levels compared to the group with lower CRP (26.5% versus 16.4% at 2 years, p=0.021) (Supplementary Figure 4A), but the cumulative incidence of NRM was comparable between the two CRP groups (Supplementary Figure 4B). In contrast, the group with lower albumin levels had significantly higher rates of relapse (28.6% versus 16.2% at 2 years, p=0.002) and NRM (16.1% versus 7.2% at 2 years, p=0.044) compared to the group with higher albumin (Supplementary Figures 4A and 4B). Age-adjusted HCT-CI scores [28] did not affect OS, relapse, or NRM in univariate analysis (Supplementary Figure 5).

Discussion

We evaluated the impact of the CHARM score on posttransplant outcomes in adults undergoing unrelated single-unit CBT. In this study, the CHARM score significantly influenced overall mortality and relapse, but not NRM, which is inconsistent with the original report [9]. Interestingly, these effects were maintained only in the subgroups of patients with AML/MDS, high and very high risk as determined by the refined DRI, and TBI conditioning regimens based on 12 Gy. Thus, our data indicate that the CHARM score predicts mortality through the stratification of relapse risk among both the entire cohort and several subgroup cohorts following unrelated single-unit CBT.

Several prognostic models for allogeneic HCT have aimed to predict transplant outcomes through the stratification of NRM [1,2,3,4,5,6,29]. The CHARM score, for example, was originally developed to estimate 1-year NRM for older patients [9]. Each element of the CHARM, including HCT-CI score, CRP, albumin, and amount of weight loss, was derived using HRs for NRM [9]. Among the previous prognostic models, the HCT-CI [1], the PAM score [2,3], and the NRM-J index [5] include components of comorbidity, whereas the TRM score alone includes serum albumin levels [6]. Previous studies demonstrated that higher pretransplant CRP levels were associated with higher NRM [30] and worse OS [31,32] among allogeneic HCT recipients. Moreover, pretransplant hypoalbuminemia, which is a marker of nutritional status and systemic chronic inflammation, is predictive of NRM after allogeneic HCT [33,34,35]. The present study has clearly demonstrated that higher CRP levels are associated with a higher rate of relapse following CBT, whereas lower albumin levels are associated with higher rates of relapse and NRM following CBT. Our previous study also showed that several factors related to inflammatory and nutritional status, including serum albumin and CRP, affected NRM after unrelated single-unit CBT [36]. The

Table 2. Multivariate analysis of overall survival, relapse, and non-relapse mortality.

	OS		Relapse		NRM	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
CHARM						
Lower (lower than -2.01)	Reference		Reference		Reference	
Higher (greater than or equal to -2.01)	1.56 (1.06-2.29)	**0.022**	1.71 (1.09-2.69)	**0.020**	1.17 (0.68-1.99)	0.560
Recipient's age						
<45 years	Reference		Reference		Reference	
≥45 years	1.80 (1.20-2.72)	**0.004**	1.10 (0.65-1.85)	0.700	2.47 (1.36-4.51)	**0.003**
Recipient's sex						
Male	Reference		Reference		Reference	
Female	0.68 (0.45-1.03)	0.069	1.05 (0.64-1.69)	0.840	0.54 (0.28-1.05)	0.072
Refined DRI						
Low/intermediate	Reference		Reference		Reference	
High/very high	2.50 (1.70-3.68)	**<0.001**	3.23 (1.99-5.25)	**<0.001**	1.31 (0.77-2.25)	0.310
Conditioning regimen						
TBI based on 10-12 Gy	Reference		Reference		Reference	
Others	0.93 (0.56-1.53)	0.776	0.62 (0.31-1.21)	0.170	1.05 (0.53-2.11)	0.870
Cord blood TNCs						
<2.5x10^7/kg	Reference		Reference		Reference	
≥2.5x10^7/kg	0.86 (0.59-1.26)	0.460	0.96 (0.61-1.51)	0.880	0.82 (0.45-1.50)	0.530
HLA mismatch						
0-1	Reference		Reference		Reference	
2-3	1.06 (0.71-1.58)	0.747	1.12 (0.68-1.85)	0.630	0.84 (0.48-1.49)	0.570

OS: Overall survival; NRM: non-relapse mortality; CHARM: Composite Health Risk Assessment Model; DRI: Disease Risk Index; TBI: total body irradiation; TNCs: total nucleated cells; HLA: human leukocyte antigen; HR: hazard ratio; CI: confidence interval. The p values in bold are statistically significant (p<0.05).

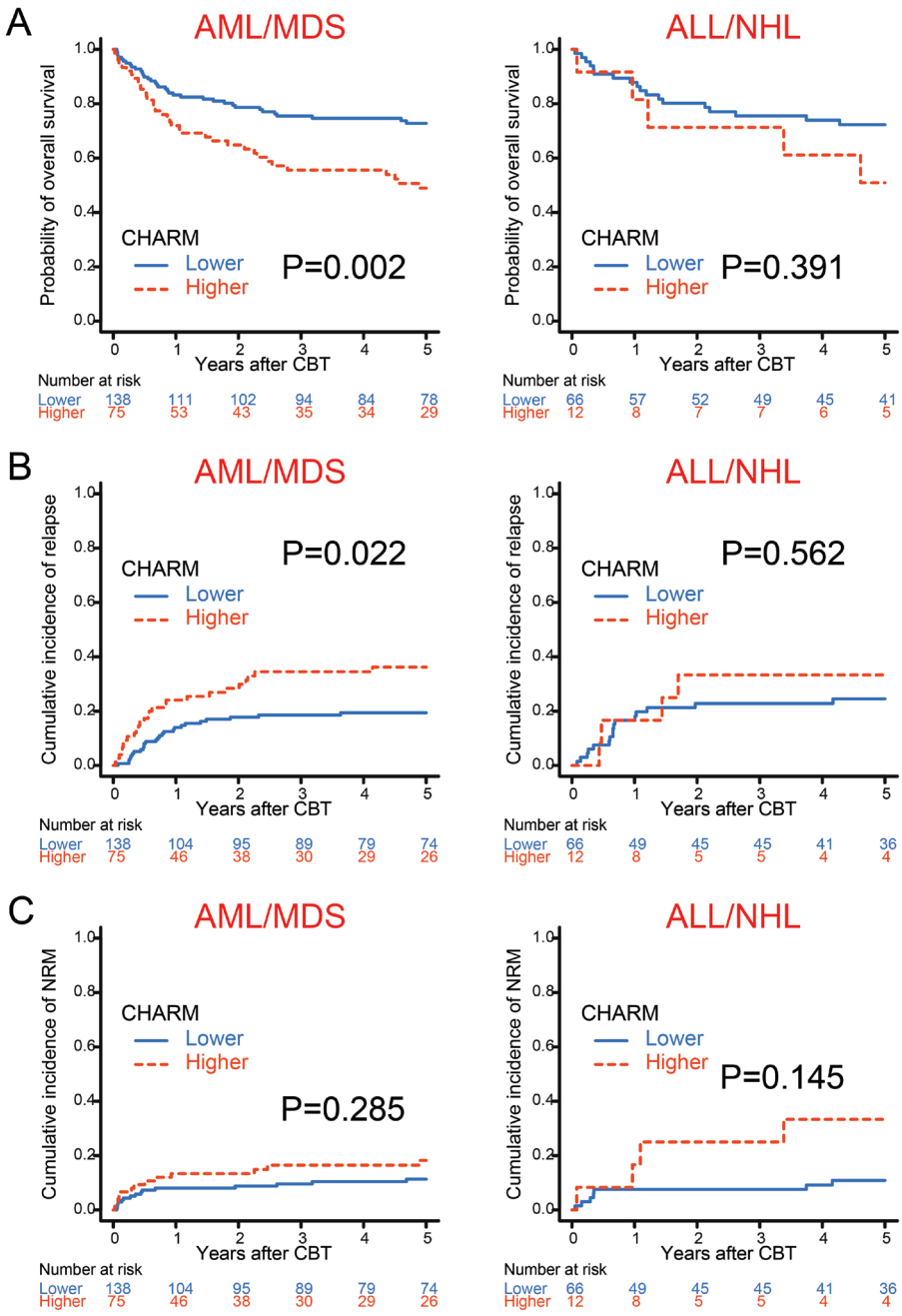

Figure 2. Unadjusted probability of overall survival (A) and cumulative incidences of relapse (B) and non-relapse mortality (C) following single-unit cord blood transplantation, stratified by the Composite Health Risk Assessment Model score within each subgroup based on disease type.

CBT: Cord blood transplantation; CHARM: Composite Health Risk Assessment Model; AML/MDS: acute myeloid leukemia/myelodysplastic syndrome; ALL/NHL: acute lymphoblastic leukemia/non-Hodgkin's lymphoma.

present study showed that the CHARM score was significantly associated with NRM in univariate analysis, but that association did not hold in multivariate analysis. The difference between our results and those of the original CHARM study might be partly due to the lower frequency of patients older than 60 years (13%) in our CBT cohort, which could contribute to the lack of an association between the CHARM and NRM in our multivariate analysis.

Unexpectedly, our study revealed that the CHARM score predicted the relapse rate rather than NRM in adult cases of unrelated single-unit CBT. Furthermore, the CHARM score's discriminative capacity for relapse was higher among higher-risk patients compared to lower-risk patients as defined by the refined DRI. Although the refined DRI has proven to be the most reliable and useful disease-specific predictor for relapse following allogeneic HCT [26], the CHARM score could stratify the relapse

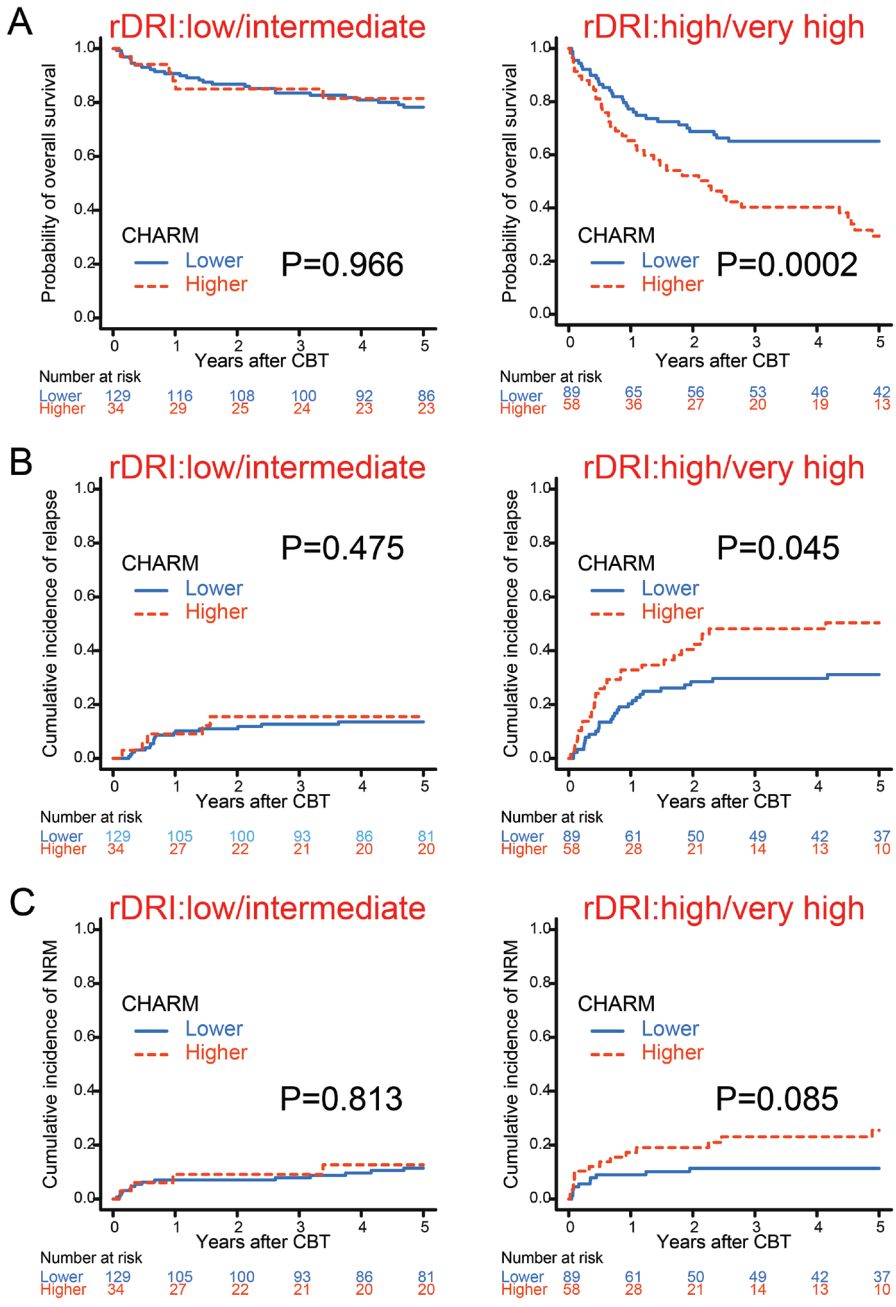

Figure 3. Unadjusted probability of overall survival (A) and cumulative incidences of relapse (B) and non-relapse mortality (C) following single-unit cord blood transplantation, stratified by the Composite Health Risk Assessment Model score within each subgroup based on disease risk status (low/intermediate vs. high/very high) according to the refined Disease Risk Index.

rDRI: Refined Disease Risk Index; CBT: cord blood transplantation; CHARM: Composite Health Risk Assessment Model.

risk, particularly among higher-risk patients, in our study. Some components of the CHARM may also be associated with disease aggressiveness. CRP has been shown to predict leukemic relapse following allogeneic HCT [37]. Hypoalbuminemia is also a component of the prognostication for AML in the AML-Composite Model [38,39], which is consistent with our results showing that the CHARM score's discriminative capacity for OS and relapse is higher in cases of myeloid malignancies compared to lymphoid malignancies. Moreover, weight reduction and serum albumin concentrations may be affected by rigorous treatment preceding allogeneic HCT, indicating that the CHARM score could influence disease recurrence following CBT. Therefore, the CHARM score could assist in selecting the best transplant strategy, such as determining the need for maintenance therapy in higher-risk patients undergoing unrelated single-unit CBT.

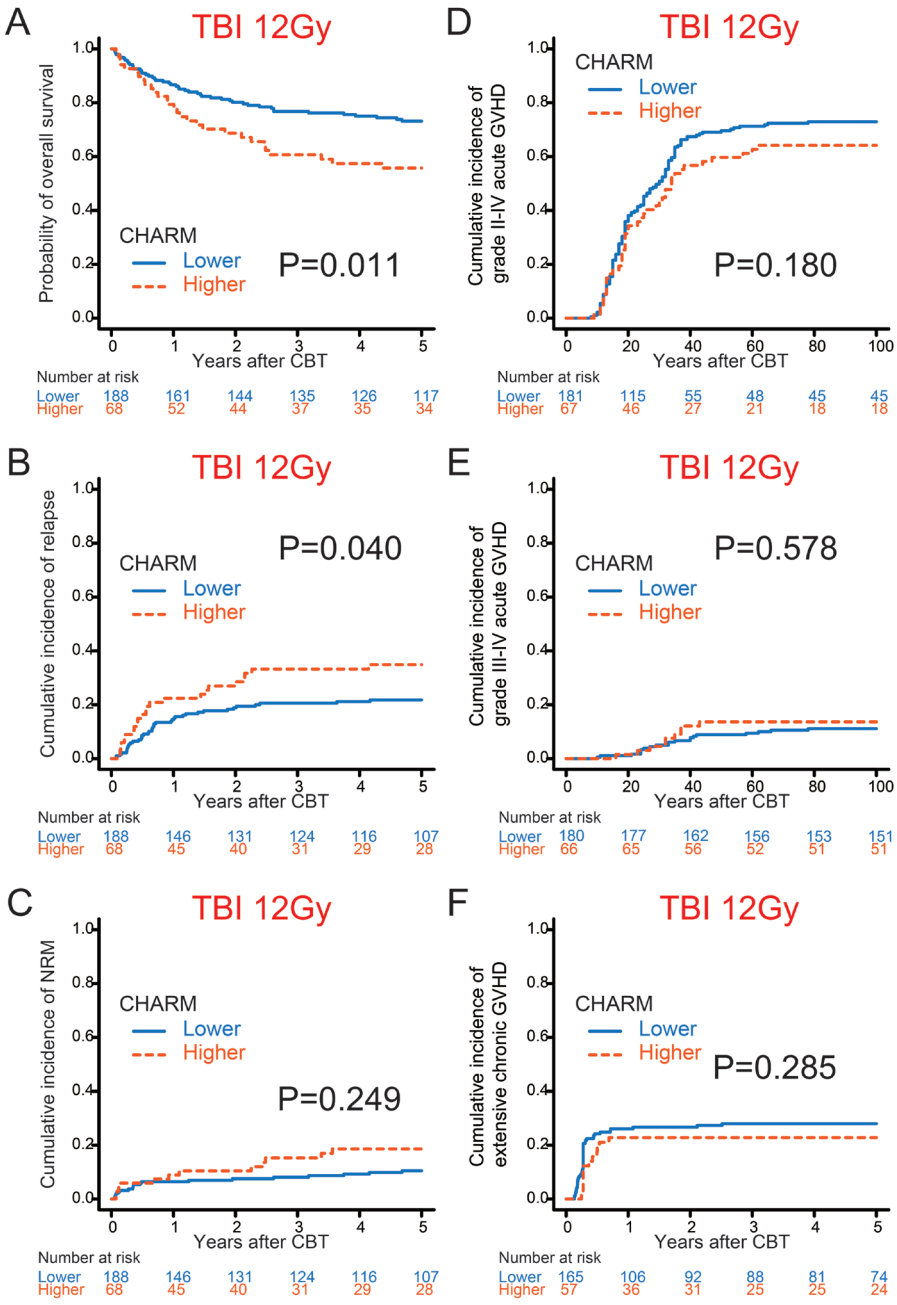

Figure 4. Unadjusted probability of overall survival (A) and cumulative incidences of relapse (B), non-relapse mortality (C), grades II to IV acute graft-versus-host disease (GVHD) (D), grades III to IV acute GVHD (E), and extensive chronic GVHD (F) following single-unit cord blood transplantation, stratified by the Composite Health Risk Assessment Model score among patients receiving total body irradiation conditioning regimens based on 12 Gy.

CBT: Cord blood transplantation; CHARM: Composite Health Risk Assessment Model; TBI: total body irradiation.

Study Limitations

We acknowledge several limitations of this study. First, this study was retrospective, was performed at a single institution in Japan, and involved a rather limited cohort of exclusively Japanese patients. Therefore, the association between the CHARM score and CBT outcomes requires further investigation in cohorts from other racial groups. Second, the original CHARM study focused on patients older than 60 years. However, the frequency of patients older than 60 years in our CBT cohort was only 13%. It is unclear whether the lower frequency of older patients contributed to the lack of association between the CHARM score and NRM in our cohort. Moreover, it remains uncertain whether our observed results are more applicable to CBT compared to adult-donor HCT. The BMT CTN 1704

prospective trial was conducted in different areas of the United States [9], and given the higher incidence and severity of GVHD in Caucasian patients compared to Japanese patients [40], both graft source and race could affect the incidence and severity of GVHD, which could contribute to the impact of the CHARM score on posttransplant outcomes.

Conclusion

Our data demonstrated that the CHARM score could predict OS through the stratification of relapse risk rather than NRM in adults undergoing unrelated single-unit CBT, which is not consistent with the original study on the CHARM score. Further validated research is needed to clarify the impact of the CHARM score on transplant outcomes in CBT.

Ethics

Ethics Committee Approval: This retrospective study was performed in compliance with the Declaration of Helsinki. The Institutional Review Board of the University of Tokyo's Institute of Science approved this retrospective study (decision no: 2024-32-0823, date: September 2, 2024).

Informed Consent: An informed consent protocol was used for the use or collection of participants' data for research purposes.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., Y.O., Y.N., S.T.; Concept: T.K.; Design: T.K.; Data Collection or Processing: S.K., M.M.-O., T.K., S.A., Y.O., Y.N., S.T.; Analysis or Interpretation: S.K., T.K.; Literature Search: S.K., T.K.; Writing: S.K., T.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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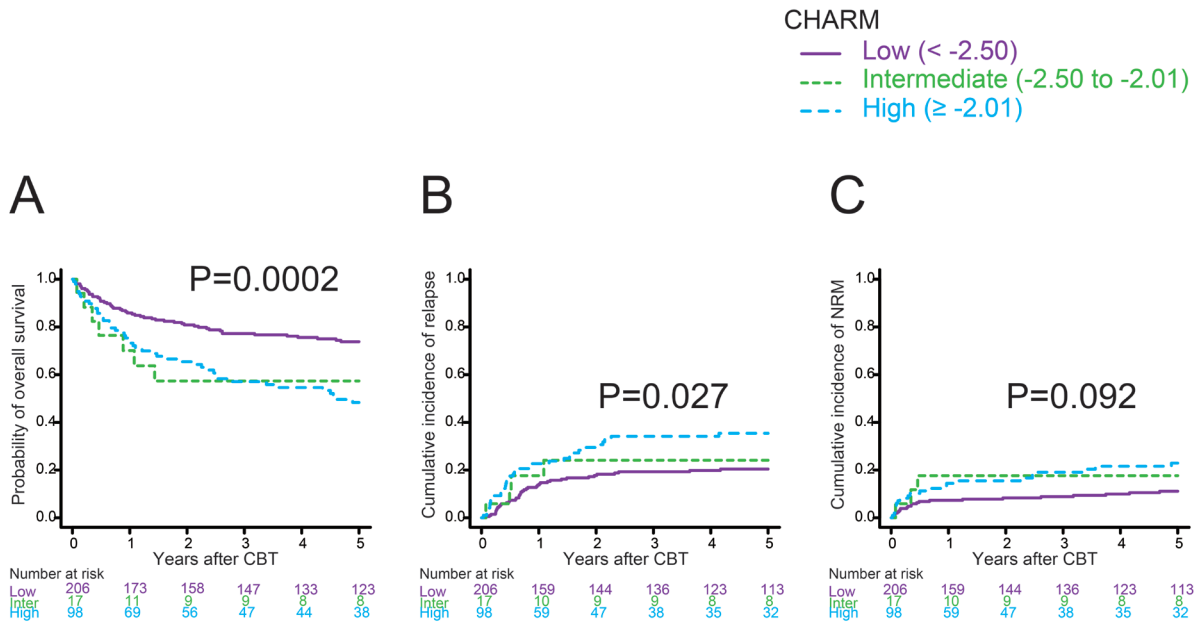
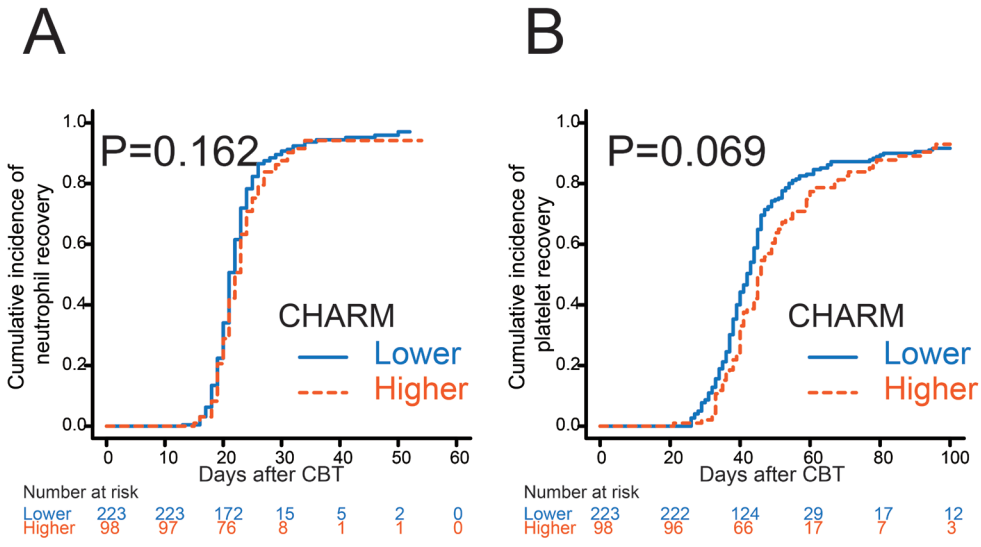


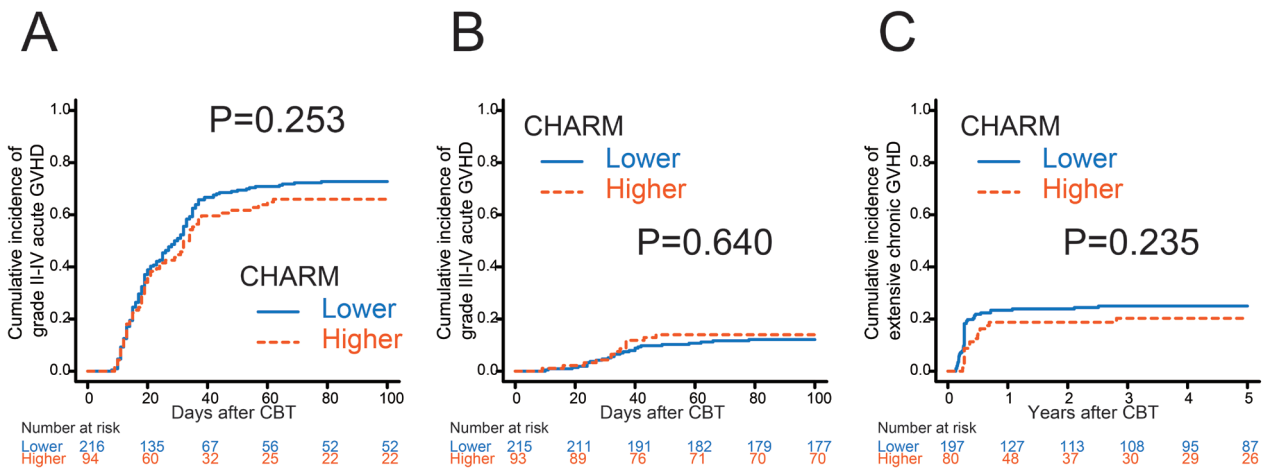
Supplementary Figure 1. Unadjusted probability of overall survival (A) and cumulative incidences of relapse (B) and non-relapse mortality (C) following single-unit cord blood transplantation, stratified by the Composite Health Risk Assessment Model score.

CHARM: Composite Health Risk Assessment Model; CBT: cord blood transplantation.



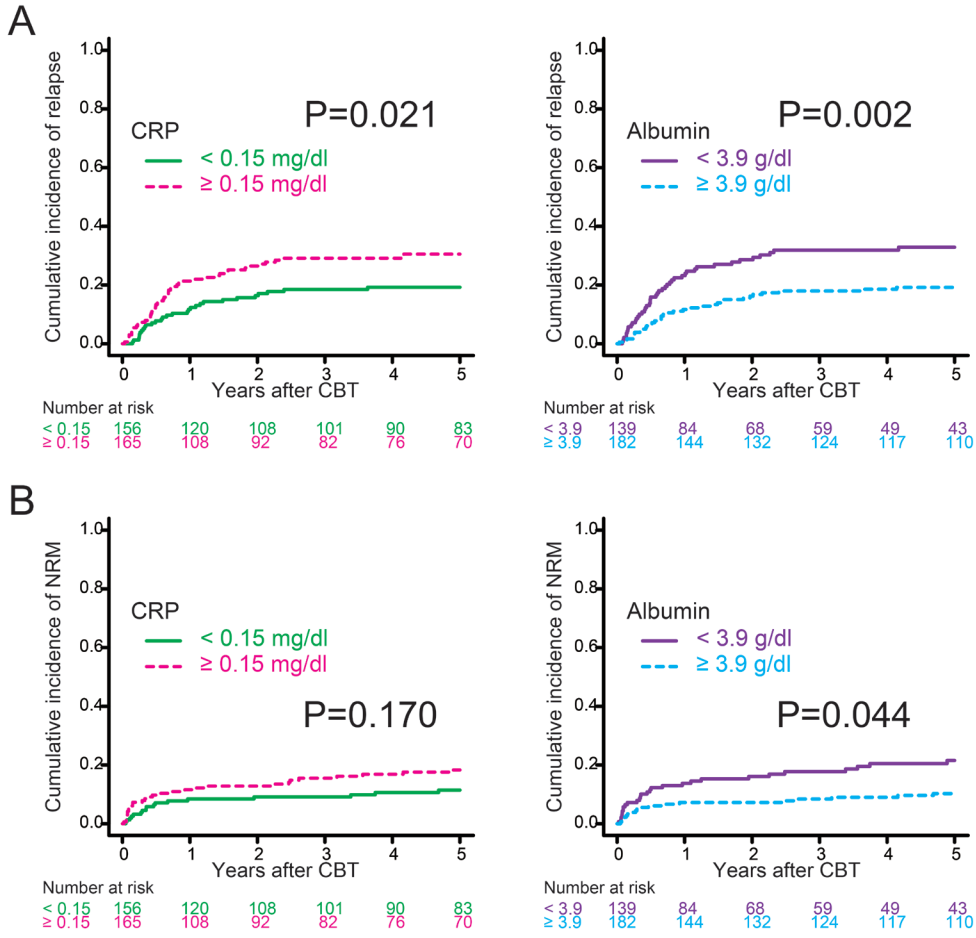
Supplementary Figure 2. Unadjusted cumulative incidences of neutrophil (A) and platelet (B) recovery following single-unit cord blood transplantation, stratified by the Composite Health Risk Assessment Model score.

CHARM: Composite Health Risk Assessment Model; CBT: cord blood transplantation.



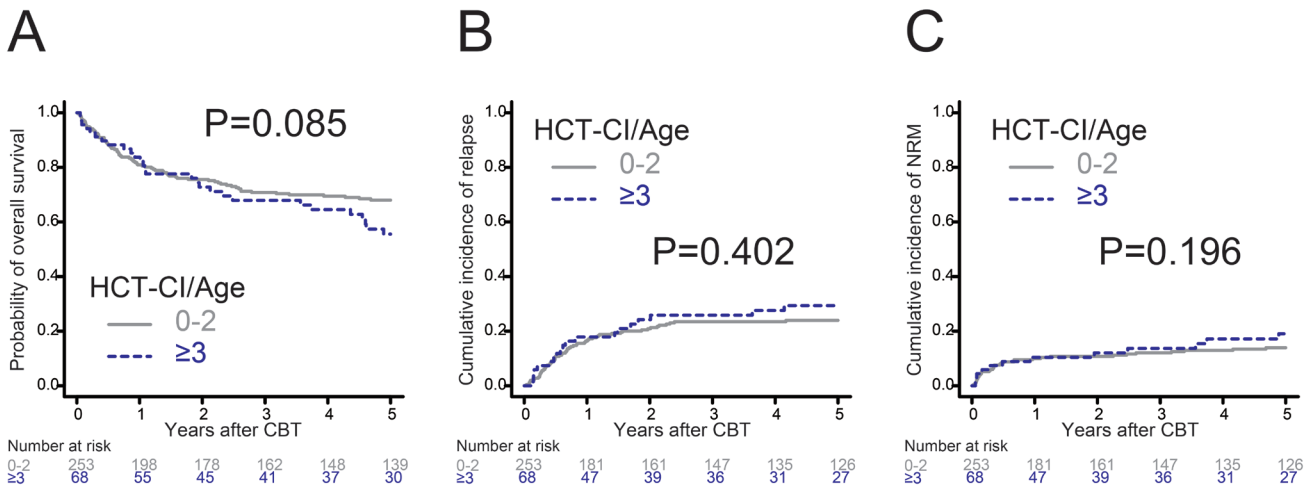
Supplementary Figure 3. Unadjusted cumulative incidences of grades II to IV acute graft-versus-host disease (GVHD) (A), grades III to IV acute GVHD (B), and extensive chronic GVHD (C) following single-unit cord blood transplantation, stratified by the Composite Health Risk Assessment Model score.

CHARM: Composite Health Risk Assessment Model; CBT: cord blood transplantation; GVHD: graft-versus-host disease.



Supplementary Figure 4. Unadjusted cumulative incidences of relapse (A) and non-relapse mortality (B) following single-unit cord blood transplantation, stratified by serum C-reactive protein and albumin levels.

CBT: Cord blood transplantation; NRM: non-relapse mortality; CRP: C-reactive protein.



Supplementary Figure 5. Unadjusted probability of overall survival (A) and cumulative incidences of relapse (B) and non-relapse mortality (C) following single-unit cord blood transplantation, stratified by the age-adjusted Hematopoietic Cell Transplantation-Specific Comorbidity Index score.

CBT: Cord blood transplantation; NRM: non-relapse mortality; HCT-CI: Hematopoietic Cell Transplantation-Specific Comorbidity Index.

Supplementary Table 1. Multivariate analysis of neutrophil and platelet recovery.

	Neutrophil recovery	p	Platelet recovery	p
	HR (95% CI)		HR (95% CI)	
CHARM				
Lower (lower than -2.01)	Reference		Reference	
Higher (greater than or equal to -2.01)	0.88 (0.69-1.12)	0.320	0.82 (0.64-1.04)	0.110
Recipient's age				
<45 years	Reference		Reference	
≥45 years	1.07 (0.84-1.36)	0.570	0.89 (0.69-1.15)	0.400
Recipient's sex				
Male	Reference		Reference	
Female	1.26 (0.99-1.60)	0.051	1.15 (0.90-1.48)	0.260
Refined DRI				
Low/intermediate	Reference		Reference	
High/very high	0.87 (0.70-1.08)	0.230	0.90 (0.71-1.16)	0.440
Conditioning regimen				
TBI based on 10-12 Gy	Reference		Reference	
Other	0.80 (0.58-1.12)	0.210	0.94 (0.64-1.37)	0.760
Cord blood TNCs				
$<2.5x10^7$/kg	Reference		Reference	
$\geq 2.5x10^7$/kg	1.20 (0.96-1.49)	0.099	1.23 (0.97-1.57)	0.083
HLA mismatch				
0-1	Reference		Reference	
2-3	0.96 (0.76-1.20)	0.730	1.06 (0.82-1.36)	0.630

CHARM: Composite Health Risk Assessment Model; DRI: Disease Risk Index; TBI: total body irradiation; TNCs: total nucleated cells; HLA: human leukocyte antigen; HR: hazard ratio; CI: confidence interval.

Supplementary Table 2. Multivariate analysis of acute and chronic graft-versus-host disease.

	Grades II-IV acute GVHD		Grades III-IV acute GVHD		Chronic GVHD		Extensive chronic GVHD	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
CHARM								
Lower (lower than -2.01)	Reference		Reference		Reference		Reference	
Higher (greater than or equal to -2.01)	0.75 (0.54-1.04)	0.091	0.76 (0.36-1.58)	0.470	0.66 (0.47-0.93)	**0.017**	0.73 (0.42-1.28)	0.280
Recipient's age								
<45 years	Reference		Reference		Reference		Reference	
≥45 years	1.44 (1.08-1.92)	**0.013**	1.64 (0.77-3.47)	0.200	0.80 (0.59-1.09)	0.170	1.43 (0.87-2.35)	0.160
Recipient's sex								
Male	Reference		Reference		Reference		Reference	
Female	1.04 (0.79-1.37)	0.730	0.76 (0.38-1.52)	0.440	0.77 (0.58-1.02)	0.070	0.54 (0.31-0.95)	0.033
Refined DRI								
Low/intermediate	Reference		Reference		Reference		Reference	
High/very high	0.91 (0.68-1.21)	0.530	2.36 (1.10-5.04)	**0.026**	0.71 (0.54-0.94)	**0.020**	0.95 (0.57-1.58)	0.850
Conditioning regimen								
TBI based on 10-12 Gy	Reference		Reference		Reference		Reference	
Others	1.24 (0.81-1.91)	0.310	1.11 (0.44-2.81)	0.810	0.53 (0.33-0.85)	**0.008**	0.31 (0.11-0.83)	**0.021**
Cord blood TNCs								
$<2.5x10^7$/kg	Reference		Reference		Reference		Reference	
$\geq 2.5x10^7$/kg	0.91 (0.68-1.21)	0.520	1.43 (0.72-2.84)	0.300	0.82 (0.62-1.07)	0.150	0.92 (0.55-1.53)	0.770
HLA mismatch								
0-1	Reference		Reference		Reference		Reference	
2-3	1.01 (0.79-.1.37)	0.730	0.51 (0.26-1.01)	0.057	1.09 (0.82-1.45)	0.540	1.14 (0.67-1.92)	0.620

CHARM: Composite Health Risk Assessment Model; GVHD: graft-versus-host disease; DRI: Disease Risk Index; TBI: total body irradiation; TNCs: total nucleated cells; HLA: human leukocyte antigen; HR: hazard ratio; CI: confidence interval. The p values in bold are statistically significant (p<0.05).