A predictive model combining clinical characteristics and nutritional risk factors for overall survival after umbilical cord blood transplantation

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Abstract

Background Umbilical cord blood transplantation (UCBT) is a curable therapy for hematological disease; however, the impact of nutritional status on UCBT outcomes remains controversial. To evaluate the joint effect of clinical characteristics and nutritional status on the prognosis of patients who underwent UCBT, we screened various factors to establish a predictive model of overall survival (OS) after UCBT.

Methods We performed an integrated clinical characteristic and nutritional risk factor analysis and established a predictive model that could be used to identify UCBT recipients with poor OS. Internal validation was performed by using the bootstrap method with 500 repetitions.

Results Four factors, including disease status, conditioning regimen, calf skinfold thickness and albumin level, were identified and used to develop a risk score for OS, which showed a positive predictive value of 84.0%. A high-risk score (≥ 2.225) was associated with inferior 3-year OS post-UCBT [67.5% (95% CI 51.1–79.4%), $P = 0.001$]. Then, we built a nomogram based on the four factors that showed good discrimination with a C-index of 0.833 (95% CI 0.743–0.922). The optimism-corrected C-index value of the bootstrapping was 0.804. Multivariate analysis suggested that a high calf skinfold thickness (≥ 20.5 mm) and a low albumin level (< 33.6 g/L) conferred poor disease-free survival (DFS).

Conclusion The predictive model combining clinical and nutritional factors could be used to predict OS in UCBT recipients, thereby promoting preemptive treatment.

Keywords Predictive model, Umbilical cord blood transplantation, Nomogram, Nutritional risk factors

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Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 2 of 13

Introduction

Umbilical cord blood transplantation (UCBT) has been performed to treat hematological and nonhematological diseases for over 30 years, with the advantages of availability, fewer restrictions associated with human leukocyte antigen (HLA) matching, a low rate of relapse for patients with positive minimal residual disease (MRD) pretransplant and a low incidence of chronic graft-versus-host disease (GvHD) [1, 2]. However, the low total nucleated cell (TNC) and CD34$^+$ cell doses in a single cord blood unit retrain the curative effect of UCBT, which may result in the occurrence of delayed engraftment, graft failure and infection that increases the risk of transplant-related mortality (TRM) [1–3].

Apart from the risk factors above [4, 5], HLA mismatch [5], cytomegalovirus (CMV) infection [4, 6], regimen-related toxicity [6], limited UCBT center experience [4] and malnutrition [7] have been associated with a high risk of mortality in UCBT recipients.

Hematopoietic stem cell transplantation (HSCT) carries nutritional risks resulting from high-dose chemotherapy alone or in combination with radiation therapy [8, 9]. In a prospective study, 21.2% of patients were at nutritional risk before HSCT according to Nutritional Risk Screening 2002 (NRS-2002), whereas the nutritional risk rate increased to 100% posttransplant [10]. Good nutritional status is beneficial for graft engraftment and immune reconstitution [11]. Furthermore, several studies have reported that disordered nutritional status during HSCT is related to inferior clinical outcomes as well as a higher complication rate during treatment, including reduced body mass index (BMI) [12], a decline in bone mineral density [13], lower serum albumin levels [14] and low vitamin D levels [13]. In recent years, a series of scales have been used to evaluate nutritional status or quality of life for predicting patient outcome, such as the Patient-Generated Subjective Global Assessment (PG-SGA) [15] and the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) [16].

There is uncertainty regarding the extent to which nutritional parameters influence clinical outcomes in UCBT recipients. Thus, in this study, we assessed the joint effect of clinical characteristics and nutritional status on overall survival (OS) post-UCBT in adult recipients and screened risk factors to build a predictive model for identifying high-risk patients for early intervention.

Materials and methods

Patients

To effectively conduct questionnaire evaluation, we performed the questionnaire investigation with only youth and adults less than 65 years of age. Between September 2018 and December 2021, a total of 80 patients who underwent UCBT at the Department of Hematology, the First Affiliated Hospital of the University of Science and Technology of China (USTC), and received systemic nutritional evaluation were included in this study. The median age of the patients was 31 years (range 17–61 years), and 46.3% (37/80) were female.

All surviving patients were followed up from the date of transplantation until June 30, 2022, and the median follow-up time was 719.0 days (range 54–1262 days). The procedures were approved by the Ethics Committee of the First Affiliated Hospital of USTC (Approval number, 2022-RE-253). Patients or guardians provided informed consent before transplantation and for the use of data for research in accordance with the Declaration of Helsinki.

Transplant protocols

The UCBT protocols were previously reported [17, 18]. The myeloablative conditioning (MAC) regimen was performed in 86.2% (69/80) of the patients, and the other 11 patients were treated with a reduced intensity conditioning (RIC) regimen. All patients were given cyclosporine (CsA) and mycophenolate mofetil (MMF) as GvHD prophylaxis after UCBT.

Nutritional status and quality of life assessments

To evaluate the validity and quality of life questionnaire in patients who received UCBT and assess the effects on survival prognosis, a series of scales were evaluated in this study at day 30 after UCBT, including the Patient-Generated Subjective Global Assessment (PG-SGA) [19], the Exercise of Self-Care Agency (ESCA) [20], the General Self-Efficacy Scale (GSES) [21], the European Cancer Research and Treatment Organization Quality of Life Questionnaire-Cancer30 (EORTC-QLQ-C30) [22] and the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) [23]. Body mass index (BMI), calf skinfold thickness, calf circumference, hand grip and albumin level were measured on the same day posttransplant, and BMI was also evaluated pretransplant. Patient weight was classified as underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), and overweight (BMI ≥ 25 kg/m^2) according to the World Health Organization [24].

Definitions

OS was calculated from the date of transplantation until death or the last follow-up, and disease-free survival (DFS) was defined as the time from transplantation to either relapse or death of any cause. In the computation of the cumulative incidence of relapse (CIR) and nonrelapse mortality (NRM), relapse and death were considered competing events [25].

Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 3 of 13

Statistical analysis

For measurement data, the normality and outliers were explored by using histogram. Estimated probabilities for OS and DFS were calculated by using the Kaplan–Meier method, and the significance levels associated with the survival curves were measured by using the log-rank test. The evaluation of CIR and NRM was performed by using Gray's test. Univariate and multivariate analyses were evaluated using the Cox proportional hazard regression model. Factors with a P value < 0.1 in the univariate analysis were subjected to multivariate analysis. To validate the model, internal verification was performed using the bootstrapping method across 500 replicates, and the optimism-corrected C-index was calculated. The "rms" package of R version 4.2.1 software was used to prepare the nomogram and bootstrap. Receiver operating characteristic (ROC) curve analyses were performed, and areas under the curve (AUCs) were calculated with OS as the actual state variable. All statistical analyses were performed using SPSS 20.0. Figures were drawn by using R software (version 4.2.1) and GraphPad Prism 9. A P value less than 0.05 was considered statistically significant.

Results

Patients

General characteristics

A total of 80 patients who underwent single-unit UCBT at our transplantation center were analyzed retrospectively. Baseline patient demographic, disease and transplant characteristics are shown in Table 1. Thirty-seven patients were female, with a median age of 32 years (range 17–61 years), and the remaining 43 were male, with a median age of 30 years (range 17–49 years). Thirty-five patients (43.8%) were diagnosed with acute myeloid leukemia (AML), 20 (25.0%) with acute lymphoblastic leukemia (ALL), 13 (16.2%) with aplastic anemia (AA), 8 (10.0%) with myelodysplastic syndrome (MDS), and the remaining 4 (5.0%) had other diseases. A total of 68.7% (55/80) of the patients exhibited complete remission (CR) before UCBT. The mean infused total nucleated cell (TNC) and mean CD34$^+$ cell values were $2.79 \pm 3.35 \times 10^7$/kg and $1.81 \pm 1.24 \times 10^5$/kg, respectively.

The data showed that 31.3% (25/80) of patients received lower high-resolution HLA compatibility ($\leq 6/10$) transplantation. The CMV infection and pulmonary infection occurred in 76.3% (61/80) and 26.3% (21/80) of patients, respectively. Furthermore, 51 patients suffered from pre-engraftment syndrome (PES).

Nutritional status and quality of life evaluation

Table 2 provides the results of the patients' nutritional status and quality of life evaluations. Fifty-one (63.8%)

Table 1 Baseline characteristics of the patients treated with UCBT (n = 80)

Characteristic	
Age, median (range)	31 (17, 61)
Sex, *n* (%)	
Female	37 (46.3)
Male	43 (53.7)
Diagnosis, *n* (%)	
AML	35 (43.8)
ALL	20 (25.0)
AA	13 (16.2)
MDS	8 (10.0)
Other	4 (5.0)
Disease status prior to transplantation, *n* (%)	
PR/NR	25 (31.3)
CR	55 (68.7)
HLA compatibility (/10), *n* (%)	
≤ 6	25 (31.3)
7–8	44 (55.0)
≥ 9	11 (13.7)
Conditioning regimen, *n* (%)	
RIC	11 (13.8)
MAC	69 (86.2)
ABO incompatibility, *n* (%)	
Identical	29 (36.3)
Major	17 (21.3)
Minor	23 (28.7)
Bidirectional	11 (13.7)
Infused TNC, (mean ± SD) × 10^7/kg	2.79 ± 3.35
Infused CD34$^+$cells, (mean ± SD) × 10^5/kg	1.81 ± 1.24
aGvHD, *n* (%)	
Grade 0–I	48 (60.0)
Grade II–IV	32 (40.0)
CMV infection posttransplant, *n* (%)	
With	61 (76.3)
Without	19 (23.7)
Pulmonary infection posttransplant, *n* (%)	
With	21 (26.3)
Without	59 (73.7)
PES, *n* (%)	
With	51 (63.7)
Without	29 (36.3)

OS overall survival, *DFS* disease-free survival, *UCBT* umbilical cord blood transplantation, *HR* hazard ratio, *CI* confidence interval, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *AA* aplastic anemia, *MDS* myelodysplastic syndrome, *PR* partial remission, *NR* nonremission, *CR* complete remission, *HLA* human leukocyte antigen, *RIC* reduced intensity conditioning, *MAC* myeloablative conditioning, *TNC* total nucleated cell, *aGvHD* acute graft-versus-host disease, *CMV* cytomegalovirus, *PES* pre-engraftment syndrome

patients had a normal BMI, 11 (13.7%) had a low BMI, and 18 (22.5%) had a high BMI. A total of 78.8% (63/80) of the patients had weight loss calculated from the initial weight before UCBT to the weight at day

Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 4 of 13

Table 2 Nutritional status and quality of life evaluation of 80 patients

Evaluation index	
BMI before transplant, *n* (%)	
Underweight	11 (13.7)
Normal	51 (63.8)
Overweight	18 (22.5)
BMI at +30 d posttransplant t, *n* (%)	
Overweight	10 (12.5)
Normal/Underweight	70 (87.5)
Ratio of BMI change, *n* (%)	
Reduced ≥ 8%	38 (47.5)
Increased/Reduced < 8%	42 (52.5)
Calf skinfold thickness, *n* (%)	
< 20.5 mm	61 (76.3)
≥ 20.5 mm	14 (17.5)
NA	5 (6.2)
Calf circumference, (mean ± SD) cm	26.76 ± 5.50
Hand grip, (mean ± SD)	21.66 ± 11.57
Albumin, g/L, *n* (%)	
< 33.6	42 (52.5)
≥ 33.6	38 (47.5)
PG-SGA, *n* (%)	
A (0–1, well-nourished)	1 (1.2)
B (2–8, suspected malnourished)	23 (28.8)
C (≥ 9, severe-malnourished)	51 (63.8)
NA	5 (6.2)
ESCA score, *n* (%)	
≥ 122.5	13 (16.3)
< 122.5	55 (687)
NA	12 (15.0)
GSES score, mean ± SD	26.22 ± 8.41
EORTC-QLQ C30 score, *n* (%)	
≥ 59.5	49 (61.3)
< 59.5	16 (20.0)
NA	15 (18.7)
FACT-BMT score, *n* (%)	
≥ 81	32 (40.0)
< 81	35 (43.8)
NA	13 (16.2)

BMI body mass index, *PG-SGA* patient-generated subjective global assessment, *ESCA* Exercise of Self-Care Agency, *GSES* General Self-Efficacy Scale, *EORTC-QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *FACT-BMT* Functional Assessment of Cancer Therapy-Bone Marrow Transplantation scale, *NA* not available

30 post-UCBT, and the mean weight loss ratio was 10.5% ± 6.9%. The median calf skinfold thickness, calf circumference and albumin level were 14.2 mm (range 4.5–30 mm), 27.5 cm (range 8.0–37.5 cm) and 33.3 g/L (range 23.6–48.2 g/L), respectively. According to the PG-SGA, 92.5% (74/80) of the patients were at high nutritional risk after UCBT (score ≥ 2), and 68.9% (51/74) of those patients were severely malnourished (score ≥ 9). The median scores on the ESCA, GSES, EORTC-QLQ C30 and FACT-BMT scales were 110 (range 23–150), 25 (range 10–58), 65 (range 43–93) and 81 (range 55–133), respectively.

Clinical outcomes

OS, DFS, aGvHD, CIR and NRM

After UCBT, 36 patients developed aGvHD, including 32 patients with grade II-IV aGvHD and 23 patients with grade III-IV aGvHD. Overall, 8 patients (10%) relapsed after UCBT, and 12 patients died of TRM. The probability of 3-year OS was 80.3% (95% CI 69.3–87.7%), and the probability of 3-year DFS was 73.2% (95% CI 61.3–81.9%) (Fig. 1A, B). The cumulative incidences of 3-year CIR and 3-year NRM were 11.5% (95% CI 5.3–20.5%) and 15.3% (95% CI 8.3–24.2%), respectively (Fig. 1C, D).

Risk factors for survival

Furthermore, we evaluated a series of parameters, including clinical characteristics, nutritional status and quality of life evaluation indexes, for a possible association with an increased risk of OS and DFS by using univariate Cox regression analysis, as shown in Table 3. The results suggested that diagnosis (AA vs. AML, HR: 4.373, 95% CI 1.169–16.359, *P* = 0.028), disease status before transplantation [partial remission (PR)/nonremission (NR) vs. CR, HR: 3.610, 95% CI 1.283–10.157, *P* = 0.015), conditioning regimen (RIC vs. MAC, HR: 3.971, 95% CI 1.351–11.672, *P* = 0.012), calf skinfold thickness (≥ 20.5 mm vs. < 20.5 mm, HR: 3.155, 95% CI 1.050–9.479, *P* = 0.041) and albumin level (< 33.6 g/L vs. ≥ 33.6 g/L, HR: 6.756, 95% CI 1.524–29.952, *P* = 0.012) were significantly associated with an increased risk of OS. PR/NR before transplantation [HR 2.635 (95% CI 1.095–6.342), *P* = 0.031], higher calf skinfold thickness [HR 2.691 (95% CI 1.016–7.128), *P* = 0.046], and low albumin level [HR 3.196 (95% CI 1.161–8.798), *P* = 0.025] were adverse prognostic factors for DFS. Subsequently, we performed multivariate Cox regression analysis for OS and DFS, and factors with a *P* value of ≤ 0.1 were included. In the multivariate analysis for OS, the PR/NR status pretransplantation had an HR of 7.948 (95% CI 1.405–44.963, *P* = 0.019), the RIC regimen had an HR of 12.707 (95% CI 1.041–155.049, *P* = 0.046), higher calf skinfold thickness had an HR of 6.940 (95% CI 1.699–28.345, *P* = 0.007) and low albumin level had an HR of 44.701 (95% CI 3.443–580.360, *P* = 0.004). The multivariate Cox regression analysis for DFS indicated that a high calf skinfold thickness and low albumin level were independent significant predictors (calf skinfold thickness: HR 3.485, 95% CI 1.180–10.289,
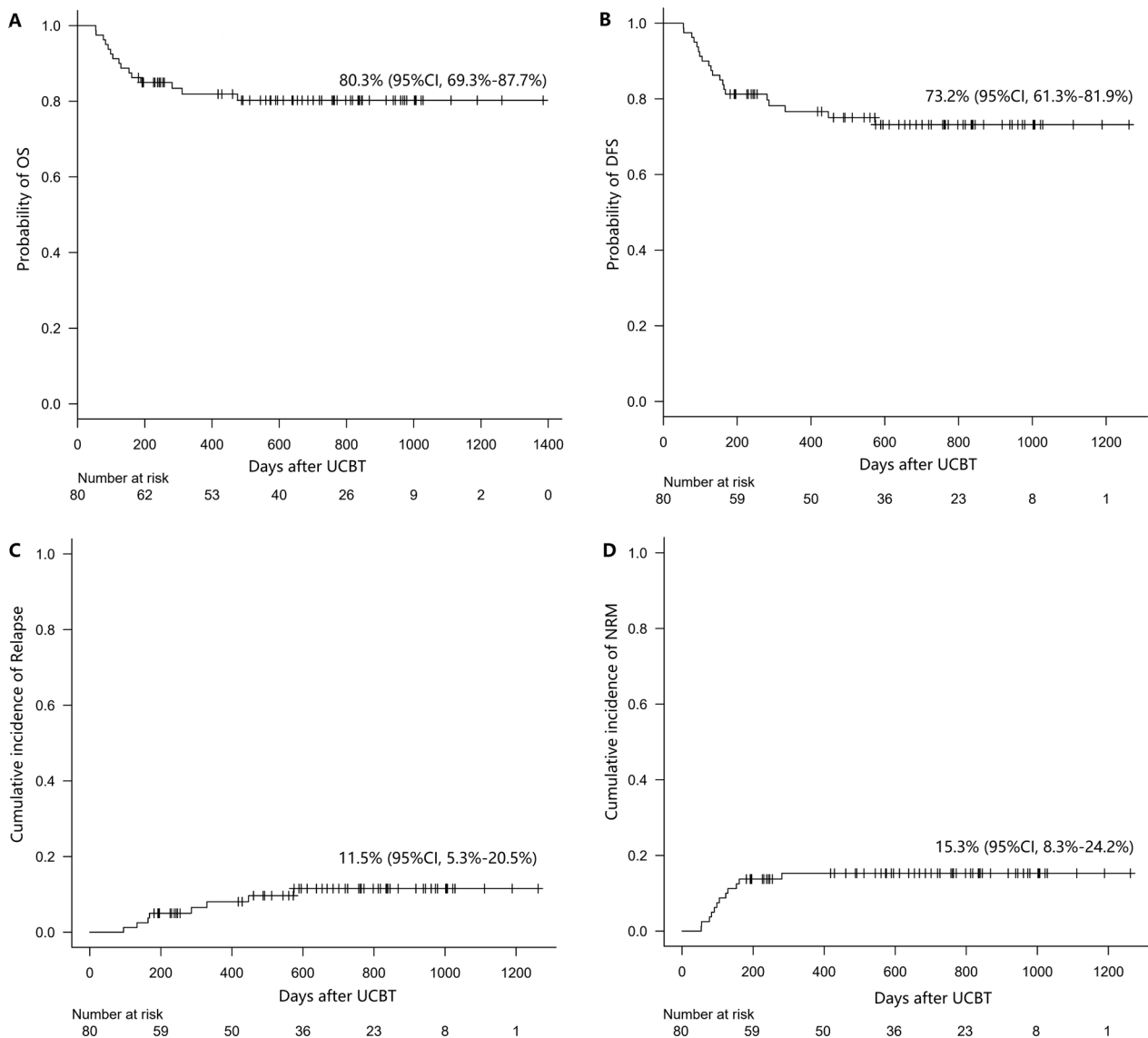
Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 5 of 13

Fig. 1 Survival of eighty UCBT recipients. **A** OS; **B** DFS; **C** CIR; **D** NRM

$P = 0.024$; albumin: HR 5.612, 95% CI 1.705–18.474, $P = 0.005$).

Development of a predictive model for OS

According to the multivariate regression analysis, disease status, conditioning regimen, calf skinfold thickness and albumin level were screened to construct a predictive model for OS (Fig. 2A). Furthermore, we calculated the risk score based on the individual expression levels of the four risk factors, where the risk score $= 1.342 \times v1 + 1.630 \times v2 + 2.603 \times v3 + 1.848 \times v4$ (Table 4). The time-dependent AUC was 0.840 (95% CI 0.734–0.946, $P < 0.001$, Fig. 2C), which suggested that the model for OS had considerable discriminative abilities.

The optimal risk score cutoff was 2.225. The patients were divided into low-risk (score < 2.225, n = 30) and high-risk groups (score ≥ 2.225, n = 45) according to the cutoff value. The high-risk patients had poorer survival than the low-risk patients [3y-OS: 67.5% (95% CI 51.1–79.4%) vs. 100%, $P = 0.001$, Fig. 3A; 3y-DFS: 62.7% (95% CI 46.3–75.4%) vs. 87.5% (95% CI 64.5–96.0%), $P = 0.014$, Fig. 3B]. The rates of 3-year CIR were similar in the two groups [low risk: 12.5% (95% CI 2.7–30.1%), high risk: 12.4% (95% CI 4.4–24.8%), $P = 0.952$]. Compared with the patients in the low-risk group, those in the high-risk group had a higher NRM rate [24.8% (95% CI 13.2–38.4%) vs. 0%, $P = 0.004$, Fig. 3D].

Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 6 of 13

Table 3 Univariate and multivariate analysis of OS in 80 patients treated with UCBT

Characteristic	OS						DFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	1.021	0.976–1.067	0.369				1.006	0.966–1.047	0.782			
Sex, female vs. male	0.570	0.195–1.668	0.305				1.199	0.499–2.883	0.685			
Diagnosis												
AML			0.247			0.535			0.655			
ALL	1.480	0.330–6.643	0.609	2.895	0.545–15.383	0.212	1.473	0.464–4.672	0.511			
AA	4.373	1.169–16.359	**0.028**	0.389	0.026–5.903	0.496	2.501	0.791–7.907	0.118			
MDS	2.759	0.503–15.135	0.242	0.904	0.122–6.728	0.922	1.553	0.322–7.497	0.584			
Other	2.685	0.298–24.187	0.379	0.083	0–31.607	0.412	1.537	0.188–12.553	0.688			
Disease status prior to transplantation												
PR/NR vs. CR	3.610	1.283–10.157	**0.015**	7.948	1.405–44.963	**0.019**	2.635	1.095–6.342	**0.031**	2.408	0.860–6.741	0.094
HLA compatibility (/10)												
≤6			0.962						0.834			
7–8	0.855	0.280–2.615	0.784				1.332	0.469–3.782	0.590			
≥9	0.934	0.181–4.289	0.935				1.451	0.346–6.093	0.611			
Conditioning regimen												
RIC vs. MAC	3.971	1.351–11.672	**0.012**	12.707	1.041–155.049	**0.046**	2.665	0.965–7.355	**0.058**	3.186	0.874–11.616	0.079
ABO incompatibility												
Identical			0.821						0.251			
Major	1.544	0.471–5.064	0.473				1.981	0.742–5.288	0.172			
Minor	0.842	0.237–2.982	0.789				0.610	0.184–2.028	0.420			
Bidirectional	0.000	0-NA	0.978				0.000	0-NA	0.976			
Infused TNC, ×10⁷/kg	1.077	0.997–1.163	**0.058**	1.219	0.975–1.524	0.082	1.070	0.990–1.156	**0.086**	1.071	0.983–1.168	0.117
Infused CD34⁺cells, ×10⁵/kg	1.046	0.705–1.551	0.824				1.002	0.697–1.443	0.990			
aGvHD, grade II-IV vs. 0-I	1.919	0.695–5.299	0.208				1.351	0.559–3.262	0.504			
CMV, with vs. without	0.880	0.280–2.765	0.827				1.298	0.434–3.884	0.641			
Pulmonary infection, with vs. without	1.521	0.520–4.453	0.444				1.353	0.519–3.523	0.536			
PES, with vs. without	1.227	0.419–3.591	0.709				0.730	0.303–1.763	0.485			
BMI before transplant												
Underweight			0.668						0.589			
Normal	2.453	0.317–18.999	0.390				0.636	0.145–2.781	0.548			
Overweight	1.917	0.199–18.430	0.573				0.562	0.162–1.942	0.362			

Tu *et al. Stem Cell Research & Therapy* (2023) 14:304

Page 7 of 13

Table 3 (continued)

Characteristic	OS								DFS							
	Univariate analysis			Multivariate analysis					Univariate analysis			Multivariate analysis				
	HR	95% CI	*P*	HR	95% CI	*P*			HR	95% CI	*P*	HR	95% CI	*P*		
BMI at + 30d posttransplant																
Overweight vs. normal/underweight	1.163	0.262–5.157	0.843						0.810	0.188–3.493	0.777					
Ratio of BMI change, reduced ≥ 8% vs. increased/reduced < 8%	2.335	0.798–6.836	0.122						1.400	0.580–3.380	0.454					
Calf skinfold thickness																
≥ 20.5 mm vs. < 20.5 mm	3.155	1.050–9.479	**0.041**	6.940	1.699–28.345	**0.007**			2.691	1.016–7.128	**0.046**	3.485	1.180–10.289	**0.024**		
Calf circumference, cm	1.014	0.918–1.119	0.790						1.012	0.930–1.100	0.785					
Hand grip	0.969	0.917–1.024	0.265						0.968	0.923–1.015	0.175					
Albumin, < 33.6 g/L vs. ≥ 33.6 g/L	6.756	1.524–29.952	**0.012**	44.701	3.443–580.360	**0.004**			3.196	1.161–8.798	**0.025**	5.612	1.705–18.474	**0.005**		
PG-SGA																
A			0.778								0.339					
B	6052.070	0–3.396E + 176	0.966						0.194	0.022–1.743	0.143					
C	9644.803	0–5.406E + 176	0.964						0.292	0.038–2.242	0.236					
ESCA, ≥ 122.5 vs. < 122.5	2.737	0.800–9.361	0.109						1.528	0.493–4.739	0.463					
GSES	1.014	0.949–1.083	0.687						0.997	0.940–1.058	0.928					
EORTC-QLQ-C30, ≥ 59.5 vs. < 59.5	33.388	0.091–12199.203	0.244						2.480	0.558–11.020	0.233					
FACT-BMT, ≥ 81 vs. < 81	1.105	0.296–4.119	0.882						1.144	0.396–3.306	0.804					

Abbreviations: Same as Tables 1 and 2

A *P* value less than 0.05 was considered statistically significant

Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304
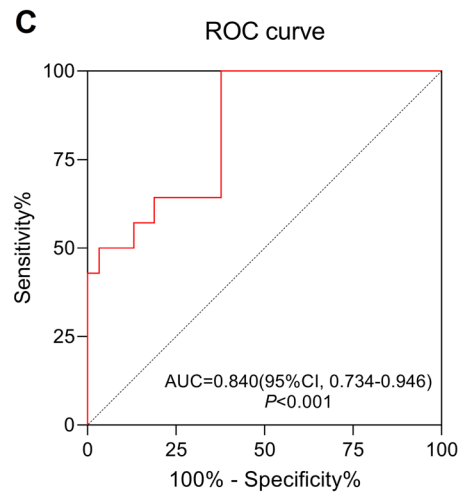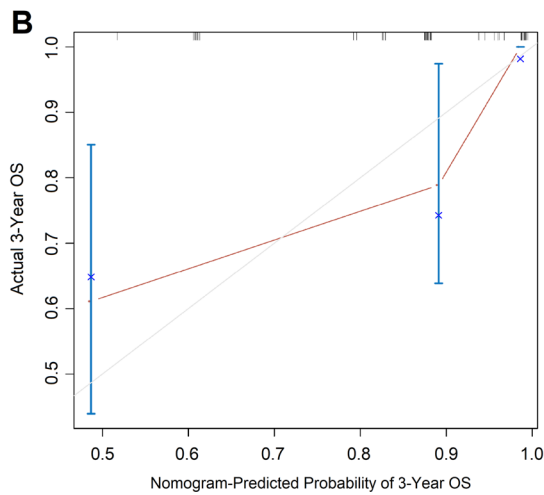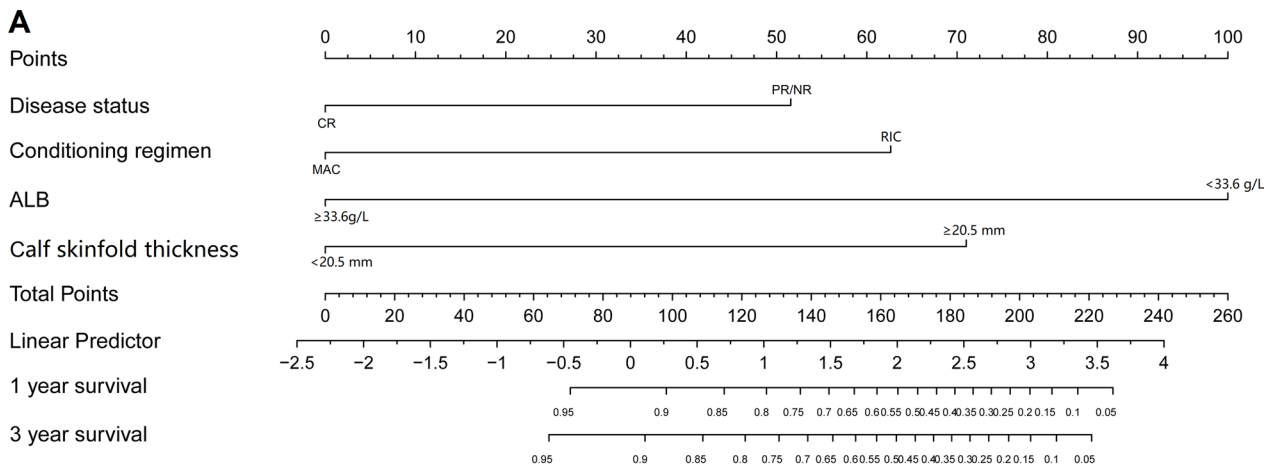
Page 8 of 13

Fig. 2 Nomogram for predicting the risk of OS. **A** Nomogram based on data from 80 patients for predicting the risk of OS; **B** The calibration curve showed the comparison between the predicted and actual 2-year OS in the internal verification; **C** ROC curve analysis of the ability of the four factors, namely disease status before UCBT, conditioning regimen, ALB and calf skinfold thickness, to predict OS. The area under the ROC curve was 0.840 (9% CI, 0734–0.948)

Table 4 A panel of four factors with predictive value for OS

Factor	AUC of ROC curve	Regression weight
v1, Disease status	0.677 (0.519–0.835)	1.342
v2, Conditioning regimen	0.621 (0.448–0.793)	1.630
v3, ALB	0.710 (0.578–0.843)	2.603
v4, Calf skinfold thickness	0.605 (0.429–0.781)	1.848

The risk score of OS for each patient was calculated by using 4 factors according to the following equation: Risk score $= 1.342 \times v1 + 1.630 \times v2 + 2.603 \times v3 + 1.848 \times v4$

Subsequently, we built a nomogram based on the panel of the model to evaluate its clinical application (Fig. 2A). The C-index value was 0.833 (95% CI 0.743–0.922). In the internal verification, the corrected C-index was 0.804, which indicated good concordance between the predicted and actual 3-year OS (Fig. 2B).
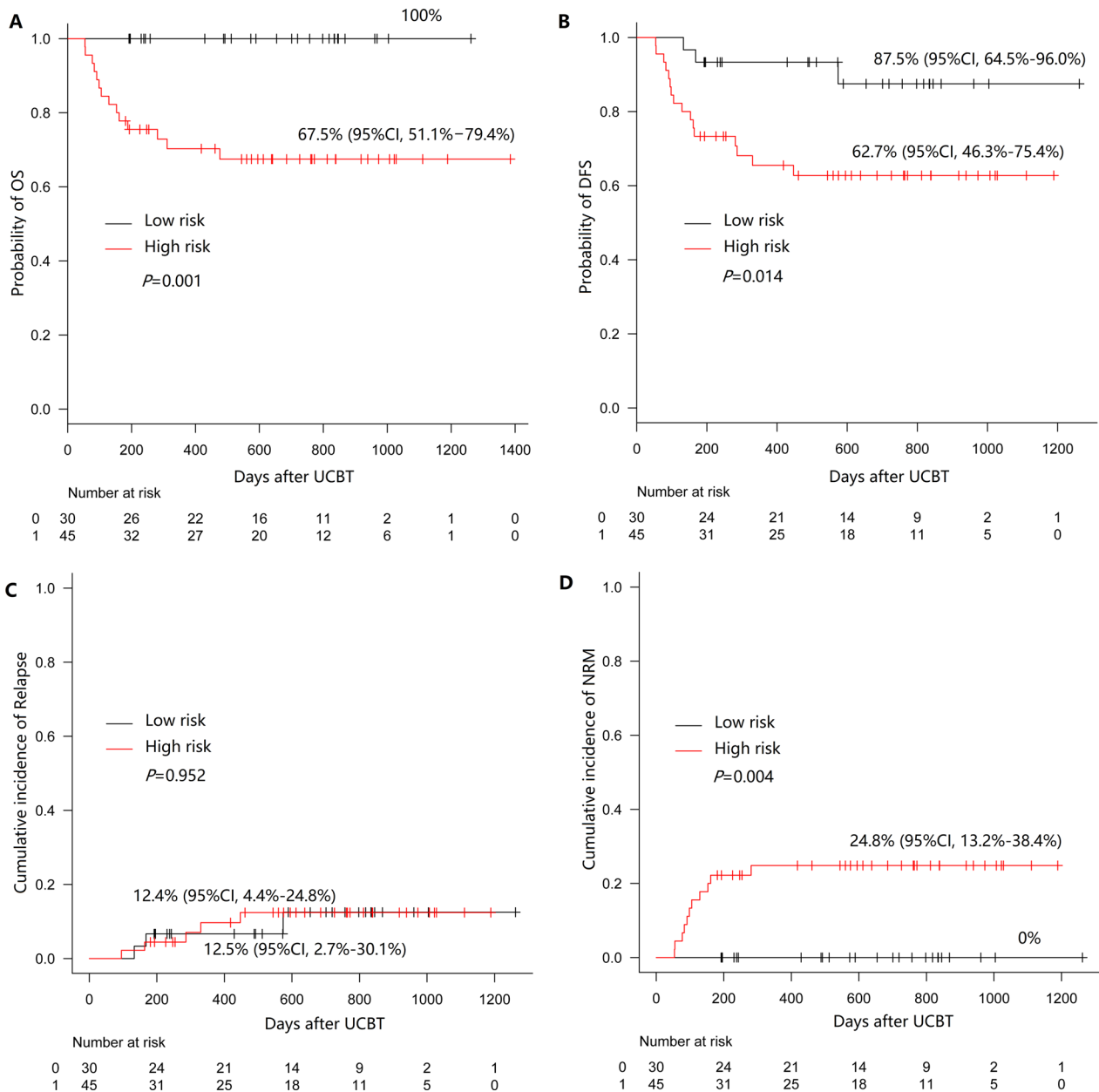
Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 9 of 13

Fig. 3 Survival outcomes according to the risk model for OS in patients who underwent UCBT (low risk: n = 30; high risk, HR: n = 45). **A** OS; **B** DFS; **C** CIR; **D** NRM

Calf skinfold thickness for predicting disease-free-survival

The cutoff point of the calf skinfold thickness was 20.5, as calculated by ROC analysis, and the patients were divided into a low calf skinfold thickness group (< 20.5, n = 61) and a high calf skinfold thickness (≥ 20.5, n = 14). The results of multivariate analysis suggested that high calf skinfold thickness was an independent risk factor for DFS. Patients with high calf skinfold thickness had inferior OS, DFS and NRM than those with low calf skinfold thickness [3y-OS: 64.3% (95% CI 34.3–83.3%) vs. 84.1% (95% CI 71.5–91.4%,

$P = 0.031$, Fig. 4A; 3y-DFS: 51.4% (95% CI 20.0–76.0%) vs. 77.0% (95% CI 63.5–86.1%), $P = 0.038$, Fig. 4B; 3y-NRM: 35.7% (95% CI 12.2–60.4%) vs. 10.1% (95% CI 4.1–19.5%), $P = 0.011$, Fig. 4D]. The CIR rates between the two groups showed no differences ($P = 0.762$, Fig. 4C).

Discussion

Chemotherapy and radiation therapy not only damage tumor cells but also significantly impair proliferative cells, such as colonic epithelial cells and lymphocytes,
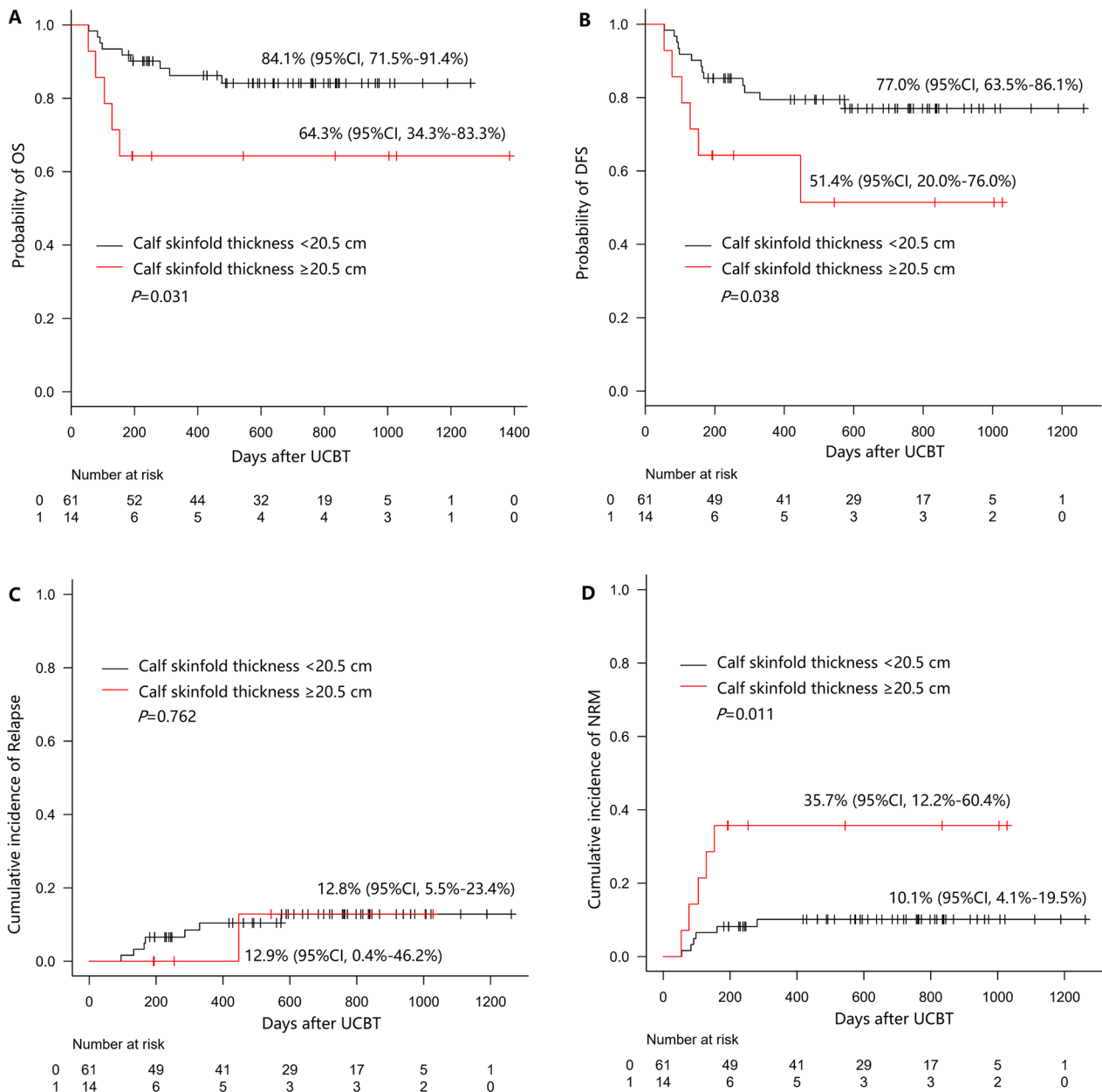
Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 10 of 13

Fig. 4 Survival outcomes according to the calf skinfold thickness (≥ 20.5 cm: n = 14; < 20.5 cm: n = 61). The results are shown for **A** OS, **B** DFS, **C** CIR, and **D** NRM

which may cause metabolic disorders and undernutrition [11]. Our results showed that 13.75% (11/80) of patients had a low BMI of < 18.5 kg/m² before UCBT, and the proportion increased to 27.5% (22/80) at day 30 post-UCBT. Moreover, 47.5% (38/80) of patients experienced weight loss of > 8% of their initial weight before transplantation. These data suggested that patients were at high nutritional risk during transplantation, which was similar to a previous report by Peng Liu et al. [10]. They enrolled 170 allo-HSCT recipients

and found that 50.46% of the patients had weight loss of more than 10% post-HSCT.

As in previous reports, various factors influence the outcome of HSCT [4, 5, 7, 26]. In addition to clinical characteristics, nutritional status plays an important role in patient survival [7, 11]. Thus, in this study, we analyzed risk factors affecting survival by combining clinical factors (such as diagnosis and disease status), nutritional and physical functional assessment indicators, including laboratory tests (albumin level), physical measures (BMI,

Tu *et al. Stem Cell Research & Therapy*   (2023) 14:304

Page 11 of 13

calf skinfold thickness, calf circumference and hand grip) and scales (PG-SGA, ESCA, GSES, EORTC-QLQ C30 and FACT-BMT). In multivariate analysis, RIC regimen, PR/NR status before transplantation, calf skinfold thickness and albumin level were independent risk factors for OS. A higher calf skinfold thickness and lower albumin level were related to poorer DFS. Then, a risk model for OS was established based on the four factors. The patients with high-risk scores (≥ 2.225) had poorer survival than those with low-risk scores [3-year OS: 67.5% (95% CI 51.1–79.4%), $P = 0.001$; 3-year DFS: 62.7% (95% CI 46.3–75.4%), $P = 0.014$] (Fig. 3).

Although many indicators were used to evaluate nutritional status in UCBT recipients, the results showed that only calf skinfold thickness and albumin level were related to survival. In our study, the above scales seem useless for predicting outcomes in patients undergoing UCBT, which suggests that laboratory indictors and physical measurements are more important than subjective scales for predicting the survival of UCBT recipients. Although we choose the same time-point of survey, the results of scales may also have bias due to differences in education and the physical and mental state of patients. Our results could simplify the evaluation type of scale and provide a practical direction for clinical work.

In previous studies, scholars reported that low albumin level was related with inflammation and poor prognosis [27–29]. Our data showed that the median level of albumin was 33.3 g/L (range 23.6–48.2 g/L) at 30 days post-UCBT, which was lower than the normal limits in our hospital (40–55 g/L). Patients had a reduced albumin levels post-transplantation, which was similar to the study reported by Stephanie et al. [30]. These patients with lower serum albumin (< 33.6 g/L) had inferior OS and DFS [OS: 67.4% (95% CI, 50.3–79.7%) vs. 94.7% (95% CI, 80.6–98.7%), $P = 0.004$; DFS: 62.3% (95% CI, 45.2–75.5%) vs. 85.4% (95% CI, 67.8–93.8%) $P = 0.018$]. Some studies identified serum albumin as a predictive marker for severe aGvHD in adult and pediatric patients post-HSCT [28, 31, 32]. The decline of albumin level may be due to impaired synthesis and increased catabolism caused by inflammation and gut damage [27, 31]. In our study, patients with lower albumin level had higher aGvHD rates; among them, 54.8% (23/42) patients developed grade II-IV aGvHD. Twenty of 23 (87.0%) aGvHD patients had gastrointestinal tract involvement.

Skinfold thickness reflects body fat level. Researchers usually assess fat mass by using the skinfold thickness at 5 to 9 body sites, such as the triceps, biceps, abdominal and calf skinfold thicknesses [10, 33]. In our center, UCBT recipients underwent insertion of central venous catheters on both upper arms. Therefore, we measured the circumference and skinfold thickness of the calf instead of the arm. In the present study, 14 patients had a higher calf skinfold thickness (≥ 20.5 mm), and among them, 57.1% (8/14) had a weight loss of > 8%. The significance of calf skinfold thickness on transplantation outcomes has not been reported. We observed that patients with a high calf skinfold thickness had an 8.289-fold risk of inferior OS than patients with a lower skinfold thickness ($P = 0.011$) and a 3.723-fold risk of poorer DFS ($P = 0.016$). Moreover, the measurement of calf skinfold thickness is a noninvasive and convenient examination that can be closely monitored in UCBT recipients.

The role of BMI in predicting outcomes is controversial. In a retrospective analysis of 2503 patients who underwent HSCT, the authors found that both underweight and obese patients had an increased NRM compared with normal-weight HSCT recipients [34]. Prasad and collaborators [35] conducted a randomized controlled phase-3 open-label trial to evaluate the effect of arm anthropometry on nutritional assessment, and the study showed that the addition of arm anthropometry (mid-upper arm circumference and triceps skinfold thickness) to BMI increased the sensitivity of nutritional evaluation. However, in our study, BMI and the decline in BMI post-HSCT showed no significant effect on OS and DFS, which was supported by other studies [36, 37].

The risk score generated from the 4 factors we identified could be used to predict OS with an AUC of 0.840 (Fig. 2C). Furthermore, based on these factors, we developed a nomogram for clinical application to help identify high-risk patients with inferior OS. Calibration plots of the nomograms showed that the nomograms performed well compared with an ideal model. By using this model, we can distinguish high-risk patients and provide early nutritional treatment.

To the best of our knowledge, this is the first study to evaluate the survival of UCBT patients by integrating clinical factors and various nutritional indexes and to build a risk model to identify high-risk patients and facilitate early interventions. However, there were some limitations in this study, such as a small sample size, a lack of a validation set, and the absence of detailed food consumption. Although internal validation by the bootstrap method with a corrected c-index of 0.804 was performed in our study, external validation is still important; thus, a multicenter clinical trial to validate our predictive model is necessary in future. Additionally, we did not investigate the specific mechanisms underlying the association between nutritional factors and UCBT outcomes, which warrants further exploration in future research.

Conclusion

In conclusion, the predictive model combining clinical and nutritional factors could be used to predict survival and stratified the survival of different groups in UCBT recipients, which may promote preemptive treatment.

Abbreviations

UCBT	Umbilical cord blood transplantation
OS	Overall survival
DFS	Disease-free survival
HLA	Human leukocyte antigen
MRD	Minimal residual disease
GvHD	Graft-versus-host disease
TNC	Total nucleated cell
TRM	Transplant-related mortality
CMV	Cytomegalovirus
HSCT	Hematopoietic stem cell transplantation
NRS-2002	Nutritional risk screening 2002
BMI	Body mass index
PG-SGA	Patient-Generated Subjective Global Assessment
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant
MAC	Myeloablative conditioning
RIC	Reduced intensity conditioning
CsA	Cyclosporine
MMF	Mycophenolate mofetil
ESCA	Exercise of self-care agency
GSES	General self-efficacy scale
EORTC-QLQ-C30	European Cancer Research and Treatment Organization Quality of Life Questionnaire-Cancer30
CIR	Cumulative incidence of relapse
NRM	Nonrelapse mortality
ROC	Receiver operating characteristic
AUC	Areas under the curve
ALL	Acute lymphoblastic leukemia
AA	Aplastic anemia
MDS	Myelodysplastic syndrome
CR	Complete remission

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Author contributions
M.T., A.H. and L.N. collected and analyzed the data and wrote the manuscript; C.Z., B.T., G.S., X.W., K.S., W.Y., P.Q. and Y.W. contributed to collect the data and treated the patients. X.Z. designed the study, analyzed the data and wrote the manuscript. M.T., A.H. and L.N. contributed equally to this study and should be considered as co-first authors. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reason-ablerequest.

Declarations

Ethics approval and consent to participate
The project titled "Analysis of risk factors of nutritional status after hematopoietic stem cell transplantation and establishment of a predictive nomogram model for survival" was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China on August 10, 2022 (Approval Number, 2022-RE-253). Patients or guardians provided informed consent before transplantation and for the use of data for research in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Tu *et al. Stem Cell Research & Therapy* (2023) 14:304

Page 13 of 13

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