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Prognostic significance of preoperative nutritional status for heart transplantation patients

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Abstract

Background The association between malnutrition and outcomes of heart transplantation (HTx) has not been well studied. The purpose of this article was to evaluate the prognostic value of three different nutrition indices in HTx, including CONUT (Controlling Nutritional Status), NRI (Nutritional Risk Index) and GNRI (Geriatric Nutritional Risk Index).

Methods A total of 438 patients who underwent THx from January 2015 to December 2020 were included in this study. The nutritional status of the patients was evaluated by CONUT, NRI and GNRI. Kaplan-Meier (KM) curves were constructed to compare the difference in overall survival (OS) between the normal and malnutrition groups in each index. Cox regression analysis was used to identify the independent risk factors of OS. The predictive power was compared by time-dependent ROC and time-dependent ccurves. Logistic regression model was used to evaluate the relationship between these three nutrition indices and postoperative clinical events.

Results 336 (76.7%), 183 (43.8%), and 190 (43.4%) patients had malnutrition according to CONUT, NRI and GNRI calculations. 102 (23.3%) patients had died at the end of follow-up. After adjustment for confounding variables, multivariate Cox analysis showed that CONUT [HR 1.286 (95%CI 1.166 ~ 1.419); $p < 0.001$], NRI [HR 0.942 (95%CI 0.923 ~ 0.962); $p < 0.001$] and GNRI [HR 0.959 (95%CI 0.939 ~ 0.979); $p < 0.001$] were all independent predictors for OS. The predictive power of CONUT score was higher than that of NRI ($p = 0.045$) and GNRI ($p < 0.001$). Regarding the postoperative complications, multivariate logistic regression model showed that malnutrition assessed by CONUT [HR 1.156 (95%CI 1.032 ~ 1.294); $p = 0.012$] and NRI [HR 1.543 (95%CI 1.008 ~ 2.362); $p = 0.046$] was independent risk factors for posttransplant infections.

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Conclusion Poor nutritional status, as assessed by CONUT, NRI and GNRI, was associated with an increased risk of mortality after HTx. CONUT displayed the highest predictive power compared to the other two indices. CONUT and NRI were also independently associated with posttransplant infections.

Keywords Malnutrition, Heart transplantation, Prognosis, Infection

Introduction

Heart transplantation (HTx) is the most effective and reliable treatment for end-stage heart failure [1]. The median survival of adult patients after HTx has exceeded 12 years and this has increased to 14.8 years among 1-year survivors [2]. There are numerous factors affecting the prognosis of HTx, including preoperative status, perioperative procedures, and postoperative events. Particularly, it is of great importance to investigate peri-operative risk factors that can be changed by timely clinical interventions to improve outcomes.

Malnourishment in advanced heart failure is frequent and may be secondary to an increased systemic inflammatory response, congestive gastropathy leading to a protein-losing enteropathy, and heightened levels of circulating catecholamines. Such patients have a higher prevalence of comorbid conditions, such as fluid and electrolyte disorders and coagulopathy, which could contribute to worse outcomes [3]. Moreover, preoperative hypoalbuminemia is strongly associated with 1-year mortality in patients undergoing HTx [4]. Despite the importance of nutrition, it is challenging to objectively evaluate the nutritional status of patients with easily measurable parameters [5]. To date, there have been several objective and simplified nutritional indices proposed such as CONUT (Controlling Nutritional Status), NRI (Nutritional Risk Index) and GNRI (Geriatric Nutritional Risk Index) [6–8]. And these indices have been used to evaluate nutrition status of hospitalized patients [9–11]. These three indices have been reported to be independent prognostic indicators in patients with some diseases, such as carcinoma, coronary artery disease, and acute myocardial infarction [8, 12, 13]. Moreover, the prognostic value of the NRI in HTx has been reported in the previous literature [14]. It showed that patients with lower NRI had significantly higher 1-year post-HTx mortality and incidence of postoperative complications. However, the operation of the subjects were performed between 1994 and 2014, so the result might be impacted by limited health technologies. In addition, it remains unclear whether the other two indices could be used to predict outcomes in patients undergoing HTx and which index would work best.

Accordingly, this study aimed to analyze the prognostic value of the above nutrition scores in patients undergoing HTx in terms of overall survival (OS) and postoperative complications.

Methods

Patients

In this study, we retrospectively analyzed patients who received HTx at Wuhan Union Hospital from January 1st, 2015, to December 31st, 2020. Exclusion criteria included multiple organ transplantation, retransplantation, patients younger than 18 years, patients with preoperative active infections and recipients with missing data. A total of 438 HTx patients were finally enrolled. The study protocol was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology. The protocol was conducted in accordance with the principles of Declaration of Helsinki. Informed consent was obtained from all patients and from legally authorized representatives/next of kin for dead patients. All methods were carried out in accordance with relevant guidelines and regulations.

Follow-up

The follow-up information of all survivors was gathered by clinical visits or telephone contact. OS was regarded as the time interval from operation to death or last contact. The follow-up was finished as of October 2nd, 2021.

Clinical variables

All patients' data were reviewed for demographic information about the recipients and donors, including age, sex, blood type, body mass index (BMI) and diagnosis. Moreover, the recipients' information also included a history of smoking, diabetes mellitus, previous cardiac surgery, left ventricular ejection fraction (LVEF), mean pulmonary pressure, systolic blood pressure and waiting time. The preoperative therapy data included implantable intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), renin-angiotensin-aldosterone system (RAAS) antagonist, beta-blockers (BB), calcium channel blocker (CCB) and diuretics. Preoperative blood biochemical indices included white blood cell count (WBC), hemoglobin (Hb), albumin, glutamic oxaloacetic transaminase (AST), creatinine (Cr), bilirubin, triglyceride (TG), low density lipoprotein (LDL), and troponin. All preoperative hematological and biochemical indicators used in the analysis were the closest available to the date of HTx.

Postoperative clinical events

We compared several postoperative clinical events between normal and malnutrition grouped according to

CONUT, NRI and GNRI, including total postoperative stay time, infection, pericardial effusion, neurological complications, kidney injury, liver injury, acute rejection and in-hospital death. Among these, postoperative infection was defined as any infection proven by a microbiological isolate and requiring intravenous antibiotic treatment during the post-HTx hospital stay. A prolonged total postoperative stay time was defined as longer than the mean of the total postoperative stay time.

Definition and of nutritional indicators

The definitions of NRI, GNRI and CONUT were as follows:

NRI = 1.519×serum albumin (g/L) + 41.7 × (actual body weight [kg]/ideal body weight [kg]) [14]. Patients were divided into four groups according to their malnutrition risk: no nutritional risk: normal (NRI > 100), mild nutritional risk (NRI 97.5–100), moderate nutritional risk (NRI 83.5–97.5), and severe nutritional risk (NRI < 83.5).

GNRI = 1.489×serum albumin (g/L) + 41.7 × (actual body weight [kg]/ideal body weight [kg]) [8]. Patients were divided into four groups according to their malnutrition risk: no nutritional risk (GNRI > 98), mild nutritional risk (GNRI 92–98), moderate nutritional risk (GNRI 82–91), and severe nutritional risk (GNRI < 82).

The CONUT score was calculated using the serum albumin concentration, peripheral lymphocyte counts and the total cholesterol concentration, as described in **Schedule 1.** [6] Patients were divided into four groups according to their malnutrition risk: no nutritional risk (CONUT 0–1), mild nutritional risk (CONUT 2–4), moderate nutritional risk (CONUT 5–8), and severe nutritional risk (CONUT 9–12).

Statistical analysis

In this study, Continuous variables are presented as the mean ± standard deviation or median [interquartile range], while categorical variables are presented as percentages. The Shapiro–Wilk test was used to determine the type of distribution of the continuous variables. The baseline characteristics of normal and malnutrition were compared using Pearson's chi-square test for categorical variables and the Mann–Whitney U rank sum test for continuous variables, which were tested and found to have a nonnormal distribution. Venn diagrams were utilized to illustrate the relationship between the three nutritional indices. The Pearson's correlation coefficients (r) were calculated as a measure of linear association among the three nutritional indices. Survival analysis was generated with the Kaplan–Meier (KM) method. Survival curves were compared using the log-rank test. The Cox proportional hazards model was used to identify independent predictors of OS. We first conducted a univariate analysis, and then conducted multivariate analysis to adjust for potential confounders. The receiver operating characteristics (ROC) curve and time-dependent areas under receiver operating characteristic curves (AUC) curve were utilized to compare the predictive power of CONUT, NRI and GNRI. Delong's test was used to compare the AUCs of two ROC-curves. In addition, we employed univariate and multivariable logistic regression to identify the predictors of postoperative clinical events. A two-tailed p-value of <0.05 was considered statistically significant. The statistical analysis was performed with SPSS 23.0, Graphpad prism 8.4.2 and R-software v.4.2.1.

Results

Clinical characteristics

Our study enrolled 438 participants who met the inclusion criteria (Fig. 1). A total of 344(78.5%) men and 94(21.5%) women were included in this study, with a mean age of 48 (range, 18–70) years. Among all patients, 274(62.5%) patients were diagnosed as non-ischemic cardiomyopathy, 89(20.3%) patients were diagnosed as ischemic cardiomyopathy, 16(3.7%) were diagnosed as congenital heart disease, and 59 (13.5%) were diagnosed as other heart diseases (valvular cardiomyopathy and arrhythmic cardiomyopathy). At the end of follow-up, 102 (23.3%) patients had died and 336(76.7%) patients were alive.

Prevalence and clinical associations of malnutrition

The histogram curves of CONUT, NRI and GNRI distribution were shown in Fig. 2. The percentage of patients with malnutrition varied from 76.7% with the CONUT score, to 43.8% with the NRI, and to 43.4% with the GNRI. By CONUT, NRI and GNRI calculations, 93 (21.2%), 134 (30.6%), and 100 (22.8%) patients had moderate to severe malnutrition, respectively. 159 (36.3%) were classified as malnourished (any degree of malnutrition) by all 3 scores, and only 81 (18.5%) were not malnourished by any score (Fig. 3). In addition, all malnutrition scores were correlated with each other (CONUT vs. NRI: r = -0.4068; CONUT vs. GNRI: r = -0.3950; NRI vs. GNRI: r = 0.9644) (Fig. 4).

We then compared the clinicopathological characteristics of patients with normal nutritional status and those with malnutrition classified by CONUT, NRI or GNRI (Table 1). The results showed that patients with high CONUT scores had more proportion of previous cardiac surgery (p = 0.012), less RAAS antagonist use (p < 0.001), lower preoperative Hb (p < 0.001), WBC (p = 0.009), serum albumin (p < 0.001) and LDL (p < 0.001) and higher bilirubin (p = 0.001). The low NRI group had a lower proportion of male (p = 0.015), diabetes mellitus (p = 0.003) and RAAS antagonist use (p = 0.003), more proportion of previous cardiac surgery (p = 0.020), and lower systolic blood pressure (p = 0.005), preoperative Hb (p < 0.001),

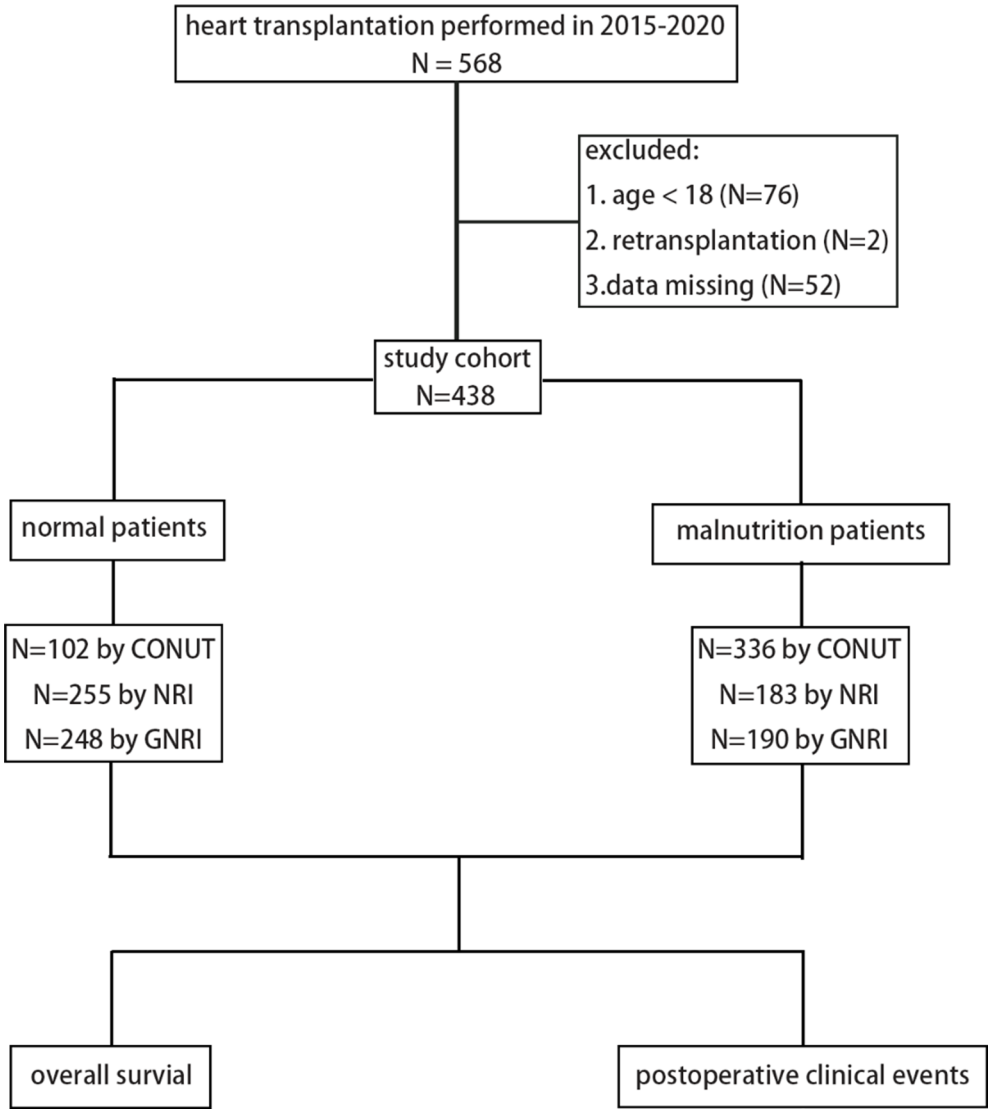

Fig. 1 Inclusion and exclusion criteria

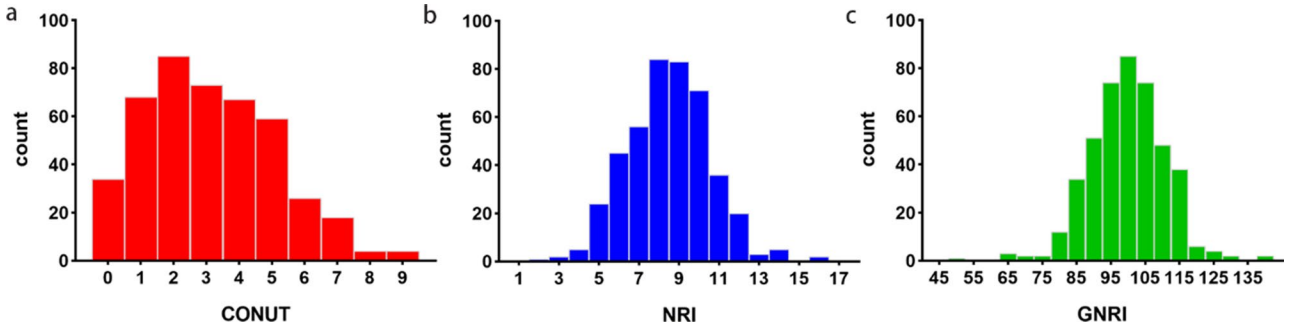

Fig. 2 Histogram plot of CONUT (**a**), NRI (**b**) and GNRI (**c**). CONUT, controlling nutritional status; NRI, nutritional risk index; GNRI, geriatric nutritional risk index

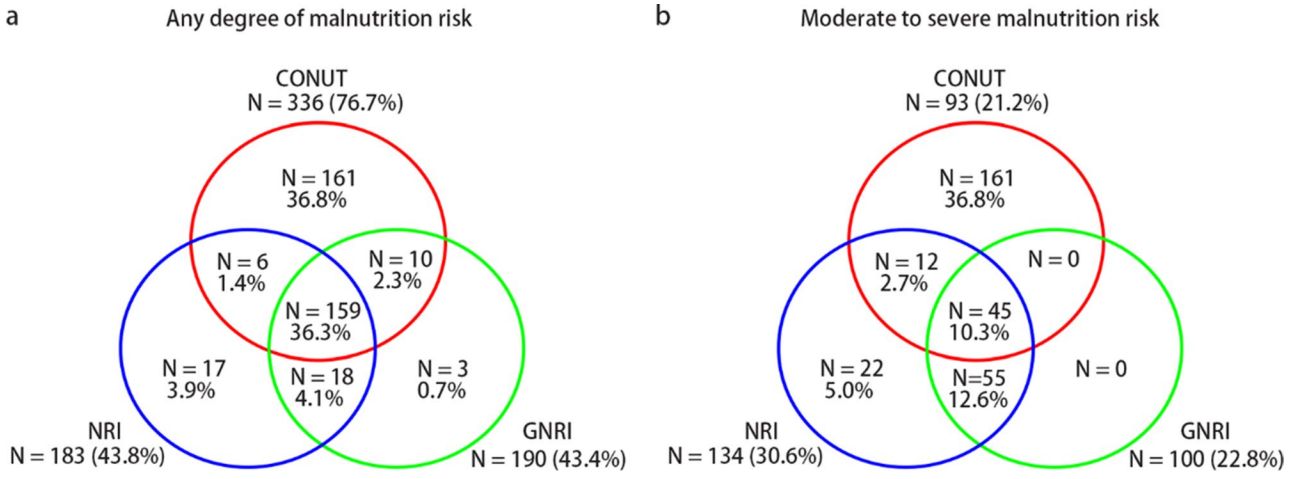

Fig. 3 Venn diagram of malnutrition risk assessed by the 3 nutritional scores. Any degree (**a**) and moderate to severe (**b**) malnutrition risk according to each nutritional score. CONUT, controlling nutritional status; NRI, nutritional risk index; GNRI, geriatric nutritional risk index

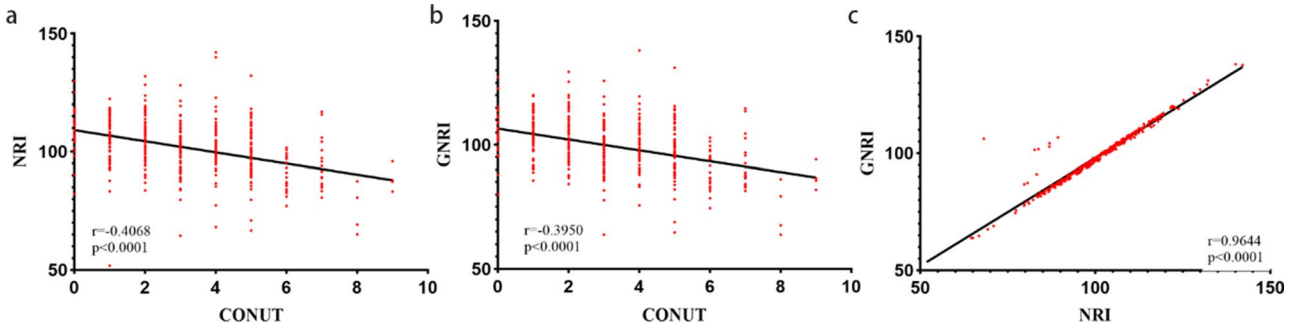

Fig. 4 The relationship between CONUT, NRI and GNRI. (**a**) The correlation between CONUT and NRI; (**b**) The correlation between CONUT and GNRI; (**c**) The correlation between NRI and GNRI. CONUT, controlling nutritional status; NRI, nutritional risk index; GNRI, geriatric nutritional risk index

serum albumin ($p<0.001$) and LDL ($p=0.001$). What's more, the low GNRI group had a lower proportion of male ($p=0.001$), diabetes mellitus ($p<0.001$) and RAAS antagonist use ($p=0.002$), more previous cardiac surgery ($p=0.024$), lower systolic blood pressure ($p<0.001$), preoperative Hb ($p<0.001$), serum albumin ($p<0.001$) and LDL ($p=0.007$).

Correlations of preoperative nutritional status with OS

The KM survival curve showed that CONUT, NRI and GNRI were all significantly associated with OS (Fig. 5, CONUT, $p<0.0001$; NRI, $p<0.0001$; and GNRI, $p=0.0036$). When calculated by CONUT, 1-year OS rates in the normal and malnutrition patients were 94.5 and 90.0%, and 5-years OS rates in the normal and malnutrition patients were 80.3 and 69.4%. When calculated by NRI, 1-year OS rates in the normal and malnutrition patients were 88.6 and 76.6%, and 5-years OS rates in the normal and malnutrition patients were 78.4 and 64.7%. When calculated by GNRI, 1-year OS rates in the normal and malnutrition patients were 86.3 and 79.2%, and 5-years OS rates in the normal and malnutrition patients were 80.0 and 67.5%.

Then, Cox regression model was used to evaluate the association between three nutritional indices and OS. Firstly, the nutritional indices were treated as continuous variables. In univariate analysis, CONUT (HR 1.432, 95% CI 1.080 ~ 1.899, $p=0.001$) was associated with OS, and the same was true for NRI (HR 0.934, 95% CI 0.916 ~ 0.952, $p<0.001$) and GNRI (HR 0.948, 95% CI 0.929 ~ 0.967, $p<0.001$) (**Schedule 2**). Regarding patient factors, age (HR 1.031, 95% CI 1.013 ~ 1.050, $p<0.001$) and history of smoking (HR 0.634, 95% CI 0.417 ~ 0.963, $p=0.033$) was significantly associated with OS. Regarding preoperative blood index, Hb (HR 0.989, 95% CI 1. 0.982 ~ 0.996, $p=0.003$) and TG (HR 0.661, 95% CI 0.411 ~ 0.908, $p=0.015$) were significantly associated with OS. In addition, preoperative IABP (HR 4.337, 95% CI 1.589 ~ 11.837, $p=0.004$) and RAAS antagonist (HR 0.630, 95% CI 0.418 ~ 0.950, $p=0.027$) were also significantly associated with OS. The results of multiple Cox regression analysis showed that CONUT (HR 1.286, 95% CI 1.166–1.419, $p<0.001$), NRI (HR 0.942, 95% CI 0.923 ~ 0.962, $p<0.001$) and GNRI (HR 0.959, 95% CI 0.939 ~ 0.979, $p<0.001$) were all independent prognostic factors for OS. (Table 2) The other independent

Table 1 Baseline characteristics of study participants grouped by preoperative nutritional risk

		Measured by CONUT			Measured by NRI			Measured by GNRI		
		Normal (≤ 1)	Malnutrition (≥ 2)	*p* value	Normal (≥ 100)	Malnutrition (< 100)	*p* value	Normal (≥ 98)	Malnutrition (< 98)	*p* value
Recipient	**Male (%)**	92(82.1)	252(77.3)	0.282	216(82.4)	128(72.7)	0.015	211(84.4)	133(70.7)	0.001
	Age, years	49.2 ± 11.8	47.5 ± 12.6	0.207	48.1 ± 11.5	47.6 ± 13.6	0.701	48.2 ± 11.6	47.6 ± 13.5	0.600
	BMI, Kg/m^2	23.6 ± 3.3	23.2 ± 8.5	0.604	24.9 ± 3.5	20.9 ± 10.6	< 0.001	25.6 ± 9.1	20.2 ± 2.5	< 0.001
	History of smoking	46(41.1)	133(40.8)	0.959	108(41.2)	71(40.3)	0.854	105(42.0)	74(39.4)	0.578
	Diagnosis			0.197			0.102			0.081
	Non-Ischemic cardiomyopathy	79(70.5)	195(59.8)		171(65.3)	103(58.5)		163(65.2)	111(59.0)	
	Ischemic cardiomyopathy	20(17.9)	69(21.2)		55(21.0)	34(19.3)		55(22.0)	34(18.1)	
	Congenital	3(2.7)	13(4.0)		6(2.3)	10(5.7)		5(2.0)	11(5.9)	
	others	10(8.9)	49(15.0)		30(11.5)	29(16.5)		27(10.8)	32(17.0)	
	Diabetes mellitus (%)	15(16.7)	50(19.5)	0.560	50(23.8)	15(10.9)	0.003	50(25.0)	15(10.2)	< 0.001
	Previous cardiac surgery (%)	20(17.9)	98(30.1)	0.012	60(22.9)	58(33.0)	0.020	57(22.8)	61(32.4)	0.024
	LVEF, %	17.6 ± 8.4	18.8 ± 10.6	0.423	18.3 ± 8.9	18.6 ± 11.6	0.803	18.3 ± 9.0	18.7 ± 11.5	0.732
	Mean pulmonary pressure, mmHg	32.9 ± 12.8	34.0 ± 14.1	0.560	34.1 ± 14.2	33.2 ± 13.5	0.608	34.0 ± 12.7	33.4 ± 15.3	0.739
	Systolic blood pressure, mmHg	105.9 ± 15.3	103.8 ± 15.3	0.221	106.5 ± 14.5	101.1 ± 15.9	0.005	106.7 ± 14.6	101.1 ± 15.6	< 0.001
	Waiting time, days	30.4 ± 12.2	28.8 ± 13.9	0.288	28.9 ± 12.5	29.7 ± 14.9	0.591	29.0 ± 12.7	29.5 ± 14.5	0.702
	Metabolic syndrome (%)	29(28.4)	124(36.9)	0.116	83(32.5)	70(38.3)	0.217	80(32.1)	73(38.6)	0.158
	Preoperative Therapy									
	ECMO (%)	0(0)	5(1.5)	0.187	2(0.8)	3(1.7)	0.363	2(0.8)	3(1.6)	0.438
	IABP (%)	0(0)	7(2.1)	0.118	2(0.8)	5(2.8)	0.089	2(0.8)	5(2.7)	0.125
	RAAS antagonist (%)	60(53.6)	116(35.6)	< 0.001	121(46.2)	55(31.3)	0.003	117(46.8)	59(31.4)	0.002
	BB (%)	89(79.5)	252(77.3)	0.634	206(78.6)	135(76.7)	0.635	198(79.2)	143(76.1)	0.434
	CCB (%)	9(11.5)	21(12.2)	0.880	21(13.5)	9(9.6)	0.360	21(14.1)	9(8.9)	0.216
	Loop diuretics (%)	103(93.6)	293(92.1)	0.607	238(91.9)	158(93.5)	0.539	229(92.7)	167(92.3)	0.862
	Spironolactone (%)	84(77.8)	259(82.0)	0.340	211(82.7)	132(78.1)	0.234	202(83.1)	141(77.9)	0.176
	Thiazides (%)	4(3.7)	16(5.4)	0.504	14(5.7)	6(3.8)	0.384	13(5.6)	7(4.1)	0.502
	Preoperative Blood Index									
	Hb, g/L	144.7 ± 17.2	129.8 ± 23.9	< 0.001	137.8 ± 20.8	127.4 ± 25.3	< 0.001	138.3 ± 20.7	127.4 ± 25.0	< 0.001
	WBC, G/L	7.7 ± 3.1	6.4 ± 2.8	0.009	6.7 ± 2.7	6.7 ± 2.9	0.928	6.7 ± 2.7	6.7 ± 6.7	0.863
	Albumin, mg/dL	41.7 ± 3.2	38.4 ± 4.5	< 0.001	41.3 ± 3.7	36.2 ± 3.8	< 0.001	41.4 ± 3.7	36.4 ± 3.9	< 0.001
	Creatinine, μmol/L	91.2 ± 30.9	101.9 ± 58.7	0.065	95.8 ± 42.8	104.1 ± 65.4	0.109	95.3 ± 38.0	104.3 ± 68.0	0.081
	Bilirubin, μmol/L	20.5 ± 11.4	31.0 ± 25.9	0.001	26.4 ± 18.6	31.2 ± 29.1	0.055	26.7 ± 18.7	30.5 ± 20.6	0.100
	AST, IU/L	32.4 ± 20.7	43.7 ± 27.9	0.208	51.9 ± 230.2	61.4 ± 234.6	0.675	51.3 ± 235.6	59.1 ± 227.2	0.790
	ALT, IU/L	38.7 ± 35.5	74.4 ± 307.1	0.221	63.3 ± 312.6	68.1 ± 175.4	0.852	65.1 ± 320.0	65.5 ± 170.1	0.988
	LDL, mmol/L	2.7 ± 0.9	2.0 ± 0.7	< 0.001	2.3 ± 0.9	2.0 ± 0.7	0.001	2.3 ± 0.9	2.0 ± 0.7	0.007
	Troponin, ng/mL	608.0 ± 3432.0	1333.0 ± 6685.1	0.273	933.2 ± 5796.4	1466.6 ± 6359.1	0.364	969.5 ± 5931.4	1384.4 ± 6160.6	0.476
	TG, mmol/L	1.1 ± 0.8	1.1 ± 0.6	0.795	1.1 ± 0.7	1.1 ± 0.7	0.843	1.1 ± 0.7	1.1 ± 0.7	0.982

Table 1 (continued)

		Measured by CONUT			Measured by NRI			Measured by GNRI		
		Normal (≤ 1)	Malnutrition (≥ 2)	*p* value	Normal (≥ 100)	Malnutrition (< 100)	*p* value	Normal (≥ 98)	Malnutrition (< 98)	*p* value
	ProBNP, pg/mL	3845.4 ± 4705.3	4778.3 ± 6320.5	0.153	3958.2 ± 4325.1	5054.5 ± 6645.2	0.114	3647.2 ± 4687.2	4536.4 ± 5946.3	0.142
	6MWT, m	158.9 ± 103.7	148.8 ± 100.2	0.661	160.4 ± 106.2	126.2 ± 70.4	0.154	161.1 ± 107.9	129.4 ± 67.1	0.144
Donor	**Age, years**	36.1 ± 12.7	35.1 ± 11.7	0.475	35.4 ± 12.0	35.4 ± 11.9	0.996	35.4 ± 12.0	35.2 ± 12.0	0.860
	Male (%)	93(83.0)	287(88.3)	0.153	31(11.8)	26(14.9)	0.358	27(10.8)	30(16.0)	0.107
	Ischemia time, min	339.6 ± 103.9	333.3 ± 108.4	0.597	335.5 ± 109.4	334.1 ± 104.2	0.894	338.1 ± 107.4	330.6 ± 107.1	0.470
Recipient/donor	**Blood-type same (%)**	88(78.6)	273(83.7)	0.358	220(84.0)	142(80.7)	0.488	209(83.6)	153(81.4)	0.421
	Donator/recipient BMI	1.0 ± 0.2	1.0 ± 0.2	0.018	0.9 ± 0.2	1.1 ± 0.2	< 0.001	0.9 ± 0.2	1.1 ± 0.2	< 0.001
	Donator/recipient age	0.8 ± 0.4	0.8 ± 0.3	0.520	0.8 ± 0.4	0.8 ± 0.4	0.376	0.8 ± 0.4	0.8 ± 0.4	0.524
	Recipient/donator sex			0.159			0.127			0.006
	male/male (%)	78(69.6)	232(71.4)		196(74.8)	114(65.1)		192(76.8)	118(63.1)	
	male/female (%)	14(12.5)	20(6.2)		20(7.6)	14(8.0)		19(7.6)	15(8.0)	
	female/male (%)	15(13.4)	55(16.9)		35(13.4)	35(20.0)		31(12.4)	39(20.9)	
	female/female (%)	5(4.5)	18(5.5)		11(4.2)	12(6.9)		8(3.2)	15(8.0)	

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICD, Implantable cardioverter-defibrillator; CRTD, cardiac resynchronization therapy defibrillator; RAAS, renin-angiotensin-aldosterone system; BB, beta-blockers; CCB, calcium channel blockers; Hb, hemoglobin; WBC, white blood cell count; AST, glutamic oxaloacetic transaminase; ALT, alanine aminotransferase; LDL, low density lipoprotein; TG, triglyceride; BNP, B-type natriuretic peptide; 6MWT, 6-minute walking test

prognostic factors were age, history of smoking and preoperative IABP use.

Furthermore, we also included the three indices as categorical variables (normal vs. malnutrition) in the COX model. And the results showed that all the three malnutrition indices were associated with OS in univariate model. Multivariate Cox regression analysis found that CONUT and NRI were still independently associated with OS. The mortality of patients with malnutrition determined by CONUT were even more than three times than that of normal patients. However, GNRI was not an independent prognostic factor in the multivariate model ($p=0.100$). (Table 2)

Comparison of CONUT, NRI and GNRI in terms of prognostic accuracy

The time-dependent ROC curves were plotted to compare the prognostic accuracies of three malnutrition indices for the prediction of OS (Fig. 6). The AUCs of CONUT, NRI, and GNRI score were 0.693 (95% CI 0.636–0.750), 0.644 (95% CI 0.586–0.703), and 0.629 (0.570–0.688), respectively. And the AUC of CONUT was significantly higher than that of NRI ($p=0.045$) and GNRI ($p<0.001$) (**Schedule 3**).

Next, the time-dependent AUC-of-ROC curves of three scoring systems for the prediction of OS were compared. The results showed that the AUC for CONUT was relatively smooth in the period three years after transplantation and tended to increase over time. The AUCs for NRI and GNRI appeared as fluctuation curves. And the AUC of CONUT tended to be higher than that of NRI and GNRI at all times tested (Fig. 7).

The association between preoperative nutritional status and postoperative clinical events

In addition to the key OS results, a number of postoperative complications were evaluated. Table 3 summarizes the adverse clinical events that occurred during the in-hospital posttransplant period in normal and malnutrition patients defined by CONUT, NRI and GNRI. Statistical analysis indicated that malnutrition calculated by CONUT corresponded to a longer total postoperative hospital stay ($p=0.015$) and a higher rate of neurological complications ($p=0.021$), kidney injury ($p=0.005$), and in-hospital death ($p=0.033$). Malnutrition calculated by NRI was related to higher rates of postoperative infection ($p=0.004$). In addition, malnutrition calculated by GNRI was related to higher rates of postoperative infections ($p=0.020$) and neurological complications ($p=0.037$).

We next performed univariate logistic analysis for these adverse clinical events (**Schedule 4 ~ 7**), and then the factors with $p<0.05$ in univariate analysis or explanatory variables reported in previous literatures were applied to multivariate logistic regression analysis. The results

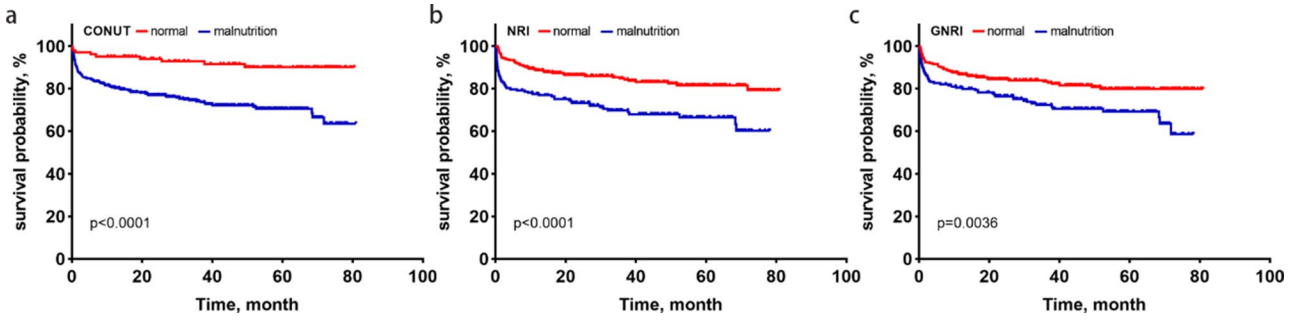

Fig. 5 Kaplan–Meier survival curves for overall survial according to three nutritional indices. The malnutrition patients calculated by CONUT (**a**), NRI (**b**) and GNRI (**c**) got a worse OS than normal patients. CONUT, controlling nutritional status; NRI, nutritional risk index; GNRI, geriatric nutritional risk index

Table 2 Multivariate COX regression analysis of OS in patients with heart transplantation

variables	CONUT		NRI		GNRI	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Nutritional indices as continuous variables						
Age	1.031 (1.013 ~ 1.049)	0.001	1.032 (1.015 ~ 1.049)	< 0.001	1.033 (1.016 ~ 1.050)	< 0.001
History of smoking	0.640 (0.418 ~ 0.981)	0.041	0.679 (0.444 ~ 1.039)	0.074	0.677 (0.442 ~ 1.036)	0.072
IABP	03.210 (1.122 ~ 9.186)	0.030	4.370 (1.562 ~ 12.223)	0.005	4.691 (1.681 ~ 13.091)	0.003
RAAS antagonist	0.702 (0.436 ~ 1.129)	0.144	0.796 (0.525 ~ 1.207)	0.283	0.767 (0.506 ~ 1.163)	0.212
Hb	1.000 (0.991 ~ 1.008)	0.918	0.998 (0.990 ~ 1.007)	0.715	0.998 (0.989 ~ 1.006)	0.596
TG	0.748 (0.486 ~ 1.150)	0.186	0.808 (0.517 ~ 1.261)	0.347	0.749 (0.482 ~ 1.164)	0.199
Waiting time	1.106 (1.002 ~ 1.030)	0.029	1.015 (1.001 ~ 1.029)	0.033	1.015 (1.001 ~ 1.029)	0.033
CONUT	1.286 (1.166 ~ 1.419)	< 0.001				
NRI			0.942 (0.923 ~ 0.962)	< 0.001		
GNRI					0.959 (0.939 ~ 0.979)	< 0.001
Nutritional indices as categorical variables						
Age	1.036 (1.018 ~ 1.054)	< 0.001	1.033 (1.016 ~ 1.051)	< 0.001	1.034 (1.016 ~ 1.051)	< 0.001
History of smoking	0.641 (0.418 ~ 0.982)	0.041	0.638 (0.417 ~ 0.975)	0.038	0.643 (0.421 ~ 0.983)	0.042
IABP	4.550 (1.627 ~ 12.720)	0.004	5.187 (1.859 ~ 14.469)	0.002	5.342 (1.919 ~ 14.877)	0.001
RAAS antagonist	0.670 (0.417 ~ 1.075)	0.097	0.758 (0.499 ~ 1.153)	0.195	0.732 (0.482 ~ 1.112)	0.144
Hb	0.999 (0.990 ~ 1.007)	0.755	0.997 (0.988 ~ 1.005)	0.444	0.996 (0.988 ~ 1.005)	0.368
TG	0.724 (0.475 ~ 1.103)	0.133	0.704 (0.458 ~ 1.082)	0.109	0.669 (0.435 ~ 1.031)	0.068
Waiting time	1.017 (1.003 ~ 1.031)	0.017	1.015 (1.001 ~ 1.030)	0.032	1.016 (1.002 ~ 1.030)	0.028
CONUT	3.124 (1.527 ~ 6.387)	0.002				
NRI			1.792 (1.179 ~ 2.722)	0.006		
GNRI					1.420 (0.935 ~ 2.157)	0.100

95% CI, 95% confidence interval; HR, hazard radio

IABP, intra-aortic balloon pump; RAAS, renin-angiotensin-aldosterone system; Hb, hemoglobin; TG, triglyceride

showed that malnutrition defined by CONUT [OR 1.156 (95%CI 1.032 ~ 1.294); $p=0.012$] and NRI [OR 1.543 (95%CI 1.008 ~ 2.362); $p=0.046$] was independent risk factor of postoperative infection, as shown in Table 4.

Discussion

Nutrition is playing an increasingly critical role in predicting the outcomes of heart diseases. Previous studies have revealed that malnutrition is an adverse prognostic factor in patients with chronic heart failure, coronary artery disease and aortic valvular disease [12, 15, 16]. However, to date, only a few studies have probed the role of malnutrition in the prognosis of heart transplantation. In the present study, we evaluated the clinical and prognostic roles of preoperative nutrition indices, including the CONUT, NRI and GNRI, in heart transplantation. The outcomes revealed that CONUT, NRI and GNRI were independent predictors of survival time following HTx. The predictive accuracy of the CONUT is highest as compare to NRI and GNRI. Additionally, CONUT and NRI were significant independent predictors of post-transplant infections.

HTx recipients tend to be end-stage of the heart failure. It has been reported that patients with heart failure often suffer from malnutrition and the prevalence varies between 5.7% and 8.1% depending on different assessment tools [17]. In this study, the prevalence of malnutrition assessed by any score was as high as 81.5% in

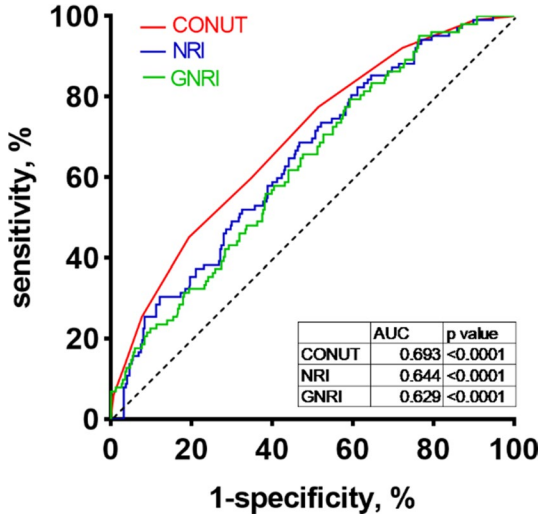

Fig. 6 Receiver operating characteristic curves for CONUT, NRI and GNRI

HTx recipients and the prevalence of moderate to severe malnutrition was even as high as 38.8%. Comprised of albumin, lymphocyte count and total cholesterol, the CONUT score is a comprehensive measure reflecting protein storage, lipid metabolism, immune system state and inflammation status. NRI, which consists of the albumin concentration and weight loss, was originally introduced in 1988 by Buzby to assess the nutrition status of adult surgical patients [15]. And the GNRI was derived from the NRI by Olivier in 2005 to assess the nutritional status of elderly patients [18]. The three indicators are simple, objective and comprehensive nutritional screening tools whose prognostic value in heart failure has been well documented. Patients with heart failure usually face anorexia and intestinal congestion and edema which could lead to insufficient nutrient intake and absorption [19]. Furthermore, chronic inflammation and neurohormonal activation in HF patients could lead to increased degradation of protein and fat tissue, and thus weight loss and even cachexia [20, 21]. Malnutrition could result in anemia, which aggravate cardiac and peripheral dysfunction and increase the risk of death [22]. In this study, we note that the hemoglobin level of malnutrition HTx reicipients (defined by any score) was significantly higher than that of normal patients. In addition, nutrient deficiencies may lead to fluid retention, inflammation, and neurohormone activation [23]. The albumin, mainly synthesized and secreted by the liver, is an index frequently used to reflect nutrient and inflammatory status, and it plays an important role in regulating osmotic pressure, antioxidant and anti-inflammatory effects of the body

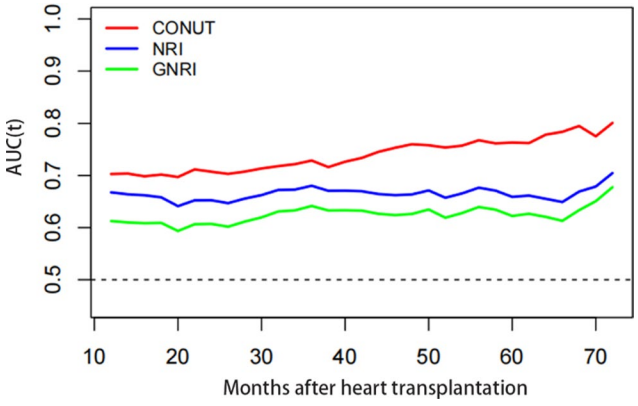

Fig. 7 Time-dependent AUC curves of CONUT, NRI and GNRI for the prediction of overall survival. The time dependence of each AUC for overall survival is shown for the period up to six years after surgery

Table 3 Postoperative clinical events grouped by CONUT, NRI, GNRI, TCBI

variables	CONUT			NRI			GNRI		
	normal (≤ 1)	malnutrition (≥ 2)	*p* value	normal (≥ 100)	malnutrition (< 100)	*p* value	normal (≥ 98)	malnutrition (< 98)	*p* value
Total postoperative stay, days	34.6 ± 15.9	40.7 ± 23.4	0.015	39.3 ± 21.3	39.2 ± 23.1	0.995	38.7 ± 21.2	40.0 ± 23.2	0.533
Postoperative infection (%)	48(49.0)	185(58.4)	0.102	122(50.2)	111(64.5)	0.004	120(50.8)	113(63.1)	0.013
Pericardial effusion (%)	60(61.9)	171(66.8)	0.384	141(65.0)	90(66.2)	0.818	137(65.9)	94(64.8)	0.840
Neurological complications (%)	2(2.0)	29(8.6)	0.021	13(5.1)	18(9.8)	0.057	12(4.8)	19(10.0)	0.037
Kidney injury (%)	7(6.9)	62(18.5)	0.005	34(13.3)	35(19.1)	0.101	34(13.7)	35(18.4)	0.180
Liver injury (%)	4(3.9)	28(8.3)	0.134	13(5.1)	19(10.4)	0.143	13(5.2)	19(10.0)	0.058
Acute rejection (%)	3(3.3)	7(2.3)	0.618	3(1.3)	7(4.3)	0.061	3(1.3)	7(4.1)	0.084
In-hospital death (%)	1(1.0)	21(6.3)	0.033	9(3.5)	13(7.1)	0.091	10(4.0)	12(6.3)	0.278

Table 4 Summary table of significance of CONUT, NRI and GNRI in postoperative clinical events

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	***p* value**	**OR (95%CI)**	***p* value**
Prolonged Total Postoperative Stay				
CONUT	1.136(1.030 ~ 1.253)	0.011	1.170 (1.037 ~ 1.321)	0.110
Postoperative Infection				
CONUT	1.211(1.093 ~ 1.341)	< 0.001	1.156(1.032 ~ 1.294)	0.012
NRI	1.805(1.209 ~ 2.695)	0.004	1.543(1.008 ~ 2.362)	0.046
GNRI	1.655(1.113 ~ 2.461)	0.013	1.465(0.959 ~ 2.238)	0.077
Kidney Injury				
CONUT	3.071(1.358 ~ 6.942)	0.007	3.689(0.817 ~ 16.746)	0.090
Neurological Complication				
CONUT	4.723(1.107 ~ 20.146)	0.036	3.690(0.832 ~ 16.361)	0.086
GNRI	2.185(1.033 ~ 4.622)	0.041	1.911(0.868 ~ 4.210)	0.108

[24]. Hypoalbuminemia in heart failure patients may cause the fluid in blood vessels transpose to the tissue, which aggravates fluid retention and tissue edema. And hypoalbuminemia is also reported to be associated with myocardial fibrosis [25]. What's more, decreased ejection fraction in end-stage heart failure patients can lead to tissue hypoperfusion and organ system dysfunction. When the kidney is involved, abnormal activation of RAAS system would further accelerate the progression of heart failure. According to the above pathophysiological process, it is not hard to understand that heart failure and malnutrition promote each other, and the heart failure of patients with malnutrition was more weight, so the prognosis is worse.

Interestingly, the predictive power of CONUT for OS was found to be higher than NRI and GNRI. We think it may be due to the following reasons. Firstly, systemic and splanchnic congestion caused by heart failure can elevate the ratio of actual body weight to ideal body weight, which is an important component of NRI and GNRI. Thus, the nutritional level could be overestimated. In this study, the proportion of malnutrition calculated by CONUT was indeed higher than that calculated by NRI and GNRI. Secondly, in addition to albumin, lymphocytes and total cholesterol were also reported to be associated with prognosis of heart transplantation [26, 27], which might be helpful to elevate the prognostic power of CONUT.

Another major finding of our study is that the CONUT and NRI are the independent risk factors for postoperative infection. The albumin molecule can bind to a wide variety of ligands, which is essential for its immunomodulatory function [28]. Hypoalbuminemia is causally linked with increased risks of both primary and secondary infection. Lymphocytes are an important cellular component in the immune response, and a drop in the preoperative lymphocyte count is closely related to the risk of developing postoperative infection in numerous conditions, such as orthotopic liver transplantation [29]. Additionally, blood lipid levels are correlated with infection [30]. Several studies have demonstrated an inverse association between total cholesterol and the incidence of nosocomial infections [31, 32]. In the CONUT scoring system, a decrease in each component is assigned a high score. This could be the reason why the higher the CONUT score is, the greater the likelihood of HTx postoperative infection. In addition, a previous study showed that weight loss could decrease the absolute count of the NKCs CD16/56 subset, which plays an important role in the innate immune system against microbial infections, and it could also lead to a significant decrease in lymphocyte counts and other immune markers [33]. Therefore, weight loss impairs immune function. This, together with the important immunomodulatory effect of serum albumin, may explain why the decrease in NRI was a risk factor for susceptibility to infections.

In addition, we noted that other factors might influence the outcomes of HTx. Recipient age, waiting time and preoperative IABP use are risk factors for all-cause death after HTx, which is consistent with the literature [34, 35]. Older recipients have a higher frequency of death, likely influenced by immunosuppression, malignancy, infection, and renal failure. Furthermore, the present study found that smoking could increase the risk of postoperative infections and prolong the length of postoperative hospital stay. The mechanism by which smoking increases infectious risk may be multifactorial. Smoking induces structural changes in the respiratory tract, including fibrosis, inflammation, increased permeability and decreased mucocillary clearance, and smoking alters the cellular concentration of CD4+cells, which are necessary for B-cell proliferation and antibody response [36]. Kidney injury is a frequent complication following HTx [37]. Our results showed that preoperative RAAS antagonist use could reduce the incidence of kidney injury after HTx, while preoperative thiazide drug use could increase it. The literature suggests that RAAS inhibitors could prevent proteinuria, kidney fibrosis and a slow decline in

renal function, and for end-stage renal disease patients, the inhibition of RAAS protects their residual renal function [38]. The effect of thiazide drugs on kidney injury following HTx may be related to their function of promoting potassium excretion from the body. Long-term low serum potassium could injure renal tubules and lead to tubular epithelial vacuolization [39].

Taken together, our findings suggest the prognostic value of nutritional indices in HTx. The CONUT, NRI and GNRI score have certain predictive values for OS and the predictive power is higher compared to NRI and GNRI. In addition, the CONUT and NRI score are independent risk factors for postoperative infection. Assessing preoperative nutritional status and identifying patients with malnutrition by CONUT, NRI or GNRI have important implications for guiding nutritional support over the perioperative period, such as albumin supplementation preoperatively, especially for those who are in a state of malnutrition. However, both obesity and underweight were found to be associated with mortality after HTx, so nutritional supplementation should be 'moderate' [40]. It is important to maintain a normal trophic level for HTx candidates. Finally, this study showed the importance of managing risk factors of HTx patients, which was similarly highlighted in the literature [41].

This study has several limitations to consider. First, as mentioned above, this was a retrospective, observational, single-center study, and inevitably, there existed an inherent risk of selection bias and information bias. Second, this study included a relatively small sample size ($n=438$). Third, we could only obtain short-term or mid-term survival because of the short follow-up duration (up to 81 months). Fourth, the values of the three indices after HTx were not be collected, so their dynamic changes were not be analysed.

Conclusions

Our study demonstrates the clinical value of the CONUT score and NRI as nutritional screening tools in HTx. Malnourished patients have a higher likelihood of postoperative infection and longer postoperative hospital stays. Given the important role of nutrition, we should closely monitor the nutrient state of patients with end-stage HF, which contributes to identifying appropriate HTx candidates who might benefit from nutritional intervention.

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Author contributions
Dr. Yao and Dr. Qian were in charge of collecting and analyzing data, and writing this manuscript. Dr Xu, Dr. Fan, and Dr. Li contributed to the discussion and provided additional advice. Dr. Chen, Dr. Shi and Dr. Dong gave their valuable and professional suggestions and guide in organizing and drafting this manuscript.

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Data availability
The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IORG No: IORG0003571). Informed consent was obtained from all patients and from legally authorized representatives/next of kin for dead patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Tatum R, Briasoulis A, Tchantchaleishvili V, et al. Evaluation of donor heart for transplantation. Heart Fail Rev. 2022;27(5):1819–27.
2. Khush KK, Cherikh WS, Chambers DC, et al. The international thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report – 2019; focus theme: Donor and recipient size match. J Heart Lung Transpl. 2019;38(10):1056–66.
3. Jain V, Karim A, Bansal A, et al. Relation of Malnutrition to Outcome following Orthotopic Heart Transplantation. Am J Cardiol. 2021;142:156–7.
4. Kato TS, Cheema FH, Yang J, et al. Preoperative serum albumin levels predict 1-year postoperative survival of patients undergoing heart transplantation. Circ Heart Fail. 2013;6(4):785–91.
5. Söderström L, Rosenblad A, Thors Adolfsson E, et al. Malnutrition is associated with increased mortality in older adults regardless of the cause of death. Br J Nutr. 2017;117(4):532–40.
6. Kuroda D, Sawayama H, Kurashige J, et al. Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. Gastric Cancer. 2018;21(2):204–12.
7. Adejumo OL, Koelling TM, Hummel SL. Nutritional Risk Index predicts mortality in hospitalized advanced heart failure patients. J Heart Lung Transpl. 2015;34(11):1385–9.
8. Jia Z, Moheb ME, Nordestgaard A, et al. The Geriatric Nutritional Risk Index is a powerful predictor of adverse outcome in the elderly emergency surgery patient. J Trauma Acute Care Surg. 2020;89(2):397–404.
9. Cheng X, Chen W, Yan J, et al. Association of preoperative nutritional status evaluated by the controlling nutritional status score with walking independence at 180 days postoperatively: a prospective cohort study in Chinese older patients with hip fracture. Int J Surg. 2023;109(9):2660–71.
10. Kang SH, Song HN, Moon JY, et al. Prevalence and prognostic significance of malnutrition in patients with acute coronary syndrome treated with percutaneous coronary intervention. Med (Baltim). 2022;101(34):e30100.
11. Minamisawa M, Seidelmann SB, Claggett B, et al. Impact of Malnutrition using Geriatric Nutritional Risk Index in Heart failure with preserved ejection fraction. JACC Heart Fail. 2019;7(8):664–75.

12. Doi S, Iwata H, Wada H, et al. A novel and simply calculated nutritional index serves as a useful prognostic indicator in patients with coronary artery disease. Int J Cardiol. 2018;262:92–8.
13. Wang XB, Chen J, Xiang BD, et al. High CONUT score predicts poor survival and postoperative HBV reactivation in HBV-related hepatocellular carcinoma patients with low HBV-DNA levels. Eur J Surg Oncol. 2019;45(5):782–7.
14. Barge-Caballero E, García-López F, Marzoa-Rivas R, et al. Prognostic value of the Nutritional Risk Index in Heart Transplant recipients. Rev Esp Cardiol (Engl Ed). 2017;70(8):639–45.
15. Bateman RM, Sharpe MD, Jagger JE et al. 36th International Symposium on Intensive Care and Emergency Medicine: Brussels, Belgium. 15–18 March 2016, Crit Care 20(Suppl 2) (2016) 94.
16. Goldfarb M, Lauck S, Webb JG, et al. Malnutrition and mortality in Frail and Non-frail older adults undergoing aortic valve replacement. Circulation. 2018;138(20):2202–11.
17. Liu J, Liu J, Wang J, et al. Prevalence and impact of malnutrition on readmission among hospitalized patients with heart failure in China. ESC Heart Fail. 2022;9(6):4271–9.
18. Bouillanne O, Morineau G, Dupont C, et al. Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr. 2005;82(4):777–83.
19. Ewid M, Sherif H, Allihimy AS, et al. AST/ALT ratio predicts the functional severity of chronic heart failure with reduced left ventricular ejection fraction. BMC Res Notes. 2020;13(1):178.
20. Sze S, Pellicori P, Kazmi S, et al. Prevalence and prognostic significance of Malnutrition using 3 Scoring systems among outpatients with heart failure: a comparison with body Mass Index. JACC Heart Fail. 2018;6(6):476–86.
21. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation. 1997;96(2):526–34.
22. Wong CC, Ng AC, Kritharides L, et al. Iron Deficiency in Heart failure: looking beyond anaemia. Heart Lung Circ. 2016;25(3):209–16.
23. Yoshihisa A, Kanno Y, Watanabe S, et al. Impact of nutritional indices on mortality in patients with heart failure. Open Heart. 2018;5(1):e000730.
24. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. Semin Dial. 2004;17(6):432–7.
25. Prenner SB, Pillutla R, Yenigalla S, et al. Serum albumin is a marker of myocardial fibrosis, adverse pulsatile aortic hemodynamics, and prognosis in heart failure with preserved ejection fraction. J Am Heart Assoc. 2020;9(3):e014716.
26. Zhou Y, Chen S, Rao Z, et al. Prediction of 1-year mortality after heart transplantation using machine learning approaches: a single-center study from China. Int J Cardiol. 2021;339:21–7.
27. Cheng RK, Deng MC, Tseng CH, et al. Risk stratification in patients with advanced heart failure requiring biventricular assist device support as a bridge to cardiac transplantation. J Heart Lung Transpl. 2012;31(8):831–8.
28. Wiedermann CJ. Hypoalbuminemia as Surrogate and Culprit of infections. Int J Mol Sci 22(9) (2021).
29. Nagai S, Yoshida A, Kohno K, et al. Peritransplant absolute lymphocyte count as a predictive factor for advanced recurrence of hepatitis C after liver transplantation. Hepatology. 2014;59(1):35–45.
30. Infection. Serum-lipids. Lancet. 1969;2(7635):1409–10.
31. Morimoto M, Nakamura Y, Atsuko S, et al. Serum total cholesterol in nosocomial infections after gastrointestinal surgery. World J Surg. 2010;34(9):2051–6.
32. Morimoto M, Nakamura Y, Yasuda Y, et al. Serum total cholesterol levels would predict nosocomial infections after gastrointestinal surgery. Indian J Surg. 2015;77(4):283–9.
33. Mehrdad M, Norouzy A, Safarian M, et al. The antiviral immune defense may be adversely influenced by weight loss through a calorie restriction program in obese women. Am J Transl Res. 2021;13(9):10404–12.
34. Bergenfeldt H, Lund LH, Stehlik J, et al. Time-dependent prognostic effects of recipient and donor age in adult heart transplantation. J Heart Lung Transpl. 2019;38(2):174–83.
35. Goldstein BA, Thomas L, Zaroff JG, et al. Assessment of Heart Transplant Waitlist Time and pre- and post-transplant failure: a mixed methods Approach. Epidemiology. 2016;27(4):469–76.
36. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med. 2004;164(20):2206–16.
37. Fortrie G, Manintveld OC, Caliskan K, et al. Acute kidney Injury as a complication of Cardiac Transplantation: incidence, risk factors, and impact on 1-year mortality and renal function. Transplantation. 2016;100(8):1740–9.
38. Zhang F, Liu H, Liu D, et al. Effects of RAAS inhibitors in patients with kidney disease. Curr Hypertens Rep. 2017;19(9):72.
39. Kudose S, Dounis H, D'Agati VD. Multicellular vacuoles in hypokalemic nephropathy. Kidney Int. 2020;97(3):618.
40. Foroutan F, Doumouras BS, Ross H, et al. Impact of pretransplant recipient body mass index on post heart transplant mortality: a systematic review and meta-analysis. Clin Transpl. 2018;32(8):e13348.
41. Simonenko M et al. Prevention and rehabilitation after heart transplantation: a clinical consensus statement of the European Association of Preventive Cardiology, Heart Failure Association of the ESC, and the European Cardio Thoracic Transplant Association, a section of ESOT. Eur J Heart Fail, https://doi.org/10.1002/ejhf.3185. 19 Jun. 2024.

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