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Prognostic Impact of Nutritional Indices in Candidates for Heart Transplantation

Kalp Nakli Adayı Hastalarında Nutrisyonel Indekslerin Prognostik Etkisi

ABSTRACT

Objective: No study has thus far evaluated the association of controlling nutritional status (CONUT) score and prognostic nutritional index (PNI) with prognosis in candidates listed for heart transplantation (HT). Therefore, in this study, we aimed to investigate the impact of these nutritional indices on prognosis in these candidates.

Methods: In this retrospective study, a total of 195 candidates for HT were included. Over a median follow-up period of 503.5 days, the patients were grouped as survivors (n=121) and non-survivors (n = 74). Malnutrition was defined as CONUT score ≥2 (CONUT-defined malnutrition) and PNI ≤38 (PNI-defined malnutrition).

Results: The CONUT-defined malnutrition was observed in 19.8% and 39.2% of the survivors and non-survivors (*P* = .003), and the PNI-defined malnutrition was observed in 7.4% and 16.2% of the survivors and non-survivors (*P* = .032). The univariate analysis revealed that the CONUT score from 0 to 2 (hazard ratio [HR]: 1.41, 95% confidence interval [CI]: 1.11–1.79, *P* =.004) and PNI from 45.5 to 54.5 (HR: 0.78, 95% CI: 0.64–0.95, *P* = .001), the CONUT-defined malnutrition (HR: 2.48, 95% CI: 1.55–3.97, *P* < .001) and the PNI-defined malnutrition (HR: 1.97, 95% CI: 1.01–3.86, *P* = .04) were associated with mortality. In the multivariate adjusted models, the CONUT-defined malnutrition was an independent predictor of mortality, whereas the PNI-defined malnutrition was not a predictor of mortality (HR: 1.92, 95% CI: 1.12–3.27, *P* = .001 and HR: 1.64, 95% CI: 0.80–3.40, *P* = .18). The log-rank test revealed that the CONUT-defined malnutrition and the PNI-defined malnutrition were associated with decrease in survival rate.

Conclusion: Although both the CONUT score and the PNI score were associated with prognosis in candidates for HT, the CONUT score was superior to the PNI score in predicting mortality.

Keywords: Controlling nutritional status score, prognostic nutritional index, malnutrition, heart transplantation, mortality

ÖZET

Amaç: Şimdiye kadar, kalp nakli adaylarında nutrisyonel durum kontrolü (CONUT) skoru ve prognostik nutrisyonel indeksi (PNI) ile prognoz arasındaki ilişkiyi değerlendiren çalışma bulunmamaktadır. Bu nedenle, bu beslenme indekslerinin kalp nakli adaylarında prognoza etkisini araştırmayı amaçladık.

Yöntem: Medyan 503.5 günlük takip süresinde, hastalar hayatta kalanlar (n = 121) ve hayatta kalmayanlar (n = 74) olarak gruplandırıldı. Malnütrisyon, CONUT skorunun ≥2 olması (CONUT-tanımlı malnütrisyon) ve PNI skorunun ≤38 olması (PNI-tanımlı malnütrisyon) olarak tanımlandı.

Bulgular: CONUT-tanımlı malnütrisyon oranı hayatta kalanlarda %19.8, hayatta kalmayanlarda %39.2 (*P* = .003); PNI-tanımlı malnütrisyon oranı hayatta kalanlarda %7.4, hayatta kalmayanlarda %16.2 (*P* = .032) olarak izlendi. Tek değişkenli analizler, CONUT skorunun 0'dan 2'ye yükselmesi (Hazard Oranı [HR]:1.41, %95 güvenlik aralığı [GA]: 1.11-1.79, *P* = .004), PNI'nin 45.5'ten 54.5'e yükselmesinin (HR:0.78, %95 CI: 0.64-0.95, *P* = 0.001), CONUT-tanımlı malnütrisyonun (HR: 2.48, %95 CI: 1.55-3.97, *P* < .001) ve PNI-tanımlı malnütrisyonun (HR: 1.97, %95 CI: 1.01-3.86, *P* = 0.04) mortalite ile ilişkili olduğunu ortaya koydu. Çok değişkenli ayarlanmış modellerde, CONUT-tanımlı malnütrisyon, mortalitenin bağımsız bir prediktörü iken, PNI-tanımlı malnütrisyon, mortalitenin prediktörü değildi (HR: 1.92, %95 CI: 1.12-3.27, P = .001 and HR: 1.64, %95 CI: 0.80-3.40, *P* = .18). Log-rank testi, CONUT tanımlı malnütrisyon ve PNI tanımlı malnütrisyonun sağkalımda azalma ile ilişkili olduğunu ortaya koydu.

Sonuç: Kalp nakli adaylarında hem CONUT skoru hem de PNI prognoz ile ilişkili olmasına rağmen, CONUT skoru mortaliteyi öngörmede PNI'den üstündür.

Anahtar Kelimeler: CONUT, PNI, nutrisyonel durum kontrolü skoru, prognostik nutrisyonel index, malnütrisyon, kalp nakli, mortalite

ORIGINAL ARTICLE
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Heart failure (HF) is a significant public health issue that results in repeated hospitalizations, decreased quality of life, and a shorter life expectancy.[1] It can be seen in up to 10% of the population over 70 years of age.[2] A left ventricular ejection fraction (LVEF) of less than 40% is considered HF with reduced ejection fraction (HFrEF).[3] Patients with HF generally have other accompanying morbidity factors, which may result in a decrease in the survival rate. Edema in the intestinal wall that develops owing to HF may cause increased problems such as decreased appetite, malabsorption, and digestive disorders in these patients.[4] This situation may lead to clinical deterioration with the acceleration of the catabolic process in the body. Malnutrition is associated with inflammation, and inflammatory parameters generally increase in patients with HF.

Malnutrition is a condition that occurs when a person's nutrition is insufficient or unbalanced and is associated with negative outcomes. A variety of methods can be used to assess an individual's malnutrition.[5] Previous studies used objective evaluation scores to assess malnutrition, such as the prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score.[6,7] Malnutrition is associated with poor outcomes in coronary syndromes, cancer, surgical procedures, contrast nephropathy, and congestive and acute HF.[8-12] However, the association of these two scores with mortality in candidates listed for heart transplant (HT) has not been investigated. Therefore, in this study, we aimed to investigate the effect of malnutrition on mortality in these candidates.

Methods

Patient population

A total of 350 patients with end-stage heart failure (ESHF) who were referred for HT evaluation were examined retrospectively between 2015 and 2020. The study included patients ≥ 18 years with LVEF ≤ 25%, and New York Heart Association (NYHA) functional class III–IV at the time of the index hospitalization as well as NYHA class II at the time of the index hospitalization but NYHA class III or IV within the previous six months. Right heart catheterization had been performed in all the patients, and index hospitalization was accepted as the hospitalization in which cardiac catheterization was performed. Patient demographics, medications, laboratories, echocardiographic and right heart catheterization findings, and co-morbidities at index hospitalization were all documented. Laboratory findings such as complete blood count, glucose, creatinine, sodium, potassium, N-terminal pro-B-type natriuretic peptide (NT-proBNP), albumin, and total cholesterol in the first 24 h of hospitalization were recorded. Transthoracic echocardiography and right heart catheterization measurements performed during the index hospitalization were also recorded. Exclusion criteria were age ≥ 70 years, inotropic dependency, need for the intra-aortic balloon pump, multiorgan failure, and comorbidities causing contraindication to HT determined by the International Society for Heart and Lung Transplantation guidelines.[13] Patients who did not have albumin, total cholesterol level, and lymphocyte count within the first 24 h of hospitalization and patients in need of urgent HT were excluded from the study. In addition, patients using statins (127 patients) were excluded from the study as using statins could affect the cholesterol level and thus the malnutrition scores. Finally, the study included 195 patients who met the inclusion criteria (Figure 1). The Ethics Committee of Koşuyolu Heart Training and Research Hospital approved the study protocol in 2017 (Approval Number: 2017.3/9-32).

Screening malnutrition

Malnutrition was assessed in patients using two indices: PNI and CONUT. PNI was calculated as follows (10 x serum albumin [g/dL] + 0.005 x total lymphocyte count [mm^3]). Malnutrition was defined as having a PNI score of ≤ 38 (PNI-defined malnutrition).[6] The CONUT score is based on serum albumin, lymphocyte count, and total cholesterol; a score of ≥ 2 indicates malnutrition (CONUT-defined malnutrition).[14]

Primary outcome

The patients were followed until December 2020. The primary endpoint was cardiac-related mortality. The patient's survival or mortality status was confirmed by clinic visit notes, phone calls, or the Ministry of Health database.

Statistical analysis

Categorical variables were expressed as frequencies with percentages for data with a normal distribution, whereas continuous variables were expressed as means and standard deviation. For data with a non-normal distribution, medians, and interquartile ranges (from 25^{th} to 75^{th}) were used. The independent t-test was used for normally distributed data and the Mann-Whitney test was used for non-normally distributed data. The chi-squared test was used to evaluate categorical variable comparisons. Spearman's correlation coefficient was used for non-parametric rank correlations.

Primary outcomes: Cardiac-related mortality during follow-up was the primary outcome. The patients were censored at the time of death or last follow-up.

Candidate predictors of mortality: Univariate and multi variate Cox proportional hazards regression analyses were used to model

ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CO	Cardiac output
CONUT	Controlling nutritional status
ESHF	End-stage heart failure
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratios
HT	Heart transplant
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAPm	Pulmonary artery mean pressure
PNI	Prognostic nutritional index
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure

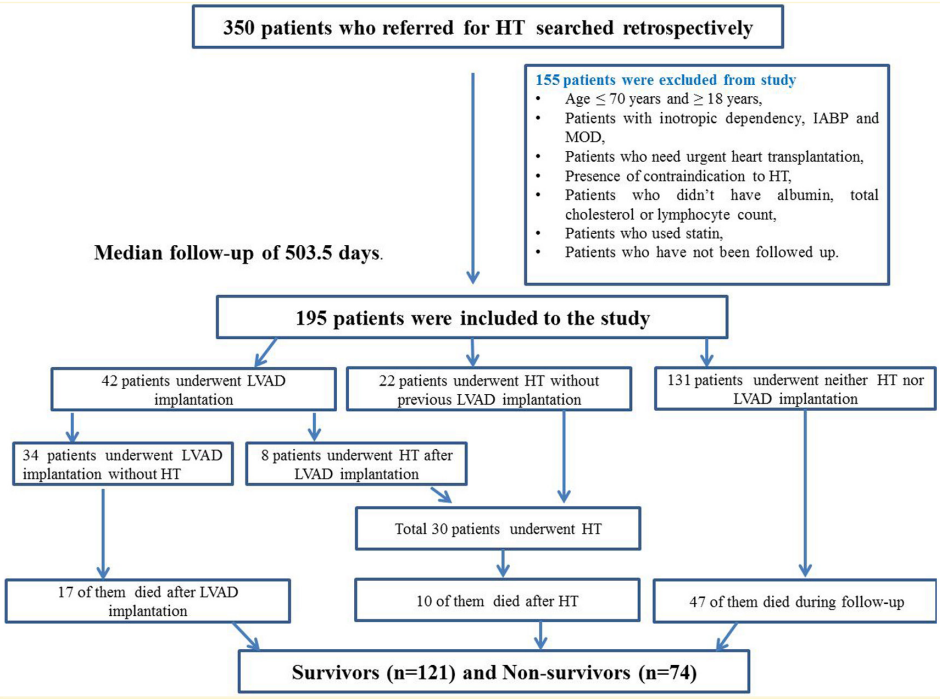

Figure 1. Consort diagram of the study population.

associations between multiple independent variables of interest and end points of interest during the follow-up period. On the basis of previous studies, putative predictors of mortality were age, NYHA, atrial fibrillation, LVEF, severe mitral regurgitation, severe tricuspid regurgitation, hemoglobin, sodium, NT-pro-BNP, pulmonary artery mean pressure (PAPm), pulmonary vascular resistance (PVR), right atrial pressure (RAP), cardiac output (CO), PNI value, CONUT value, and the presence of malnutrition according to PNI and CONUT. The unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the risk of death during the follow-up period were calculated using univariate and multivariate Cox regression analyses. Furthermore, model performance metrics such as the likelihood ratio and adjusted R2 value were calculated. The patients were divided into two groups according to their PNI and CONUT scores; those who had malnutrition and those who did not. With stratification based on main predictor variables, two different survival analyses (for CONUT and for PNI) and the Kaplan-Meier curve were used to display differences in mortality between the groups. To compare differences between groups, the log-rank test was used. In the multivariate analysis, two different models according to malnutrition assessment were used to find the relationship between candidate malnutrition scores and mortality. Model 1 (for CONUT; both continuous and categorical) and Model 2 (for PNI, both continuous and categorical) were adjusted with candidate predictors of multivariate analysis for mortality, which were selected according to univariate screening. When the two-sided *P* value was .05, differences were considered statistically significant. R-studio version 4.00 (R Statistical Software, Institute for Statistics and Mathematics, Vienna, Austria) and SPSS version 24.0 (IBM Corp., Armonk, NY, USA) were used for all statistical analyses.

Results

The study included 195 HT candidates in total. Cardiac mortality was regarded as a primary outcome. Over a median follow-up of 503.5 days (interquartile range [IQR] = 115.25–1003.25) days, 42 (21.5%) patients underwent left ventricular assist device (LVAD) implantation when awaiting HT, and 30 (15.3%) patients underwent HT; 17 patients died after LVAD implantation, 10 patients died after HT, and a total of 74 (37.7%) deaths occurred during the follow-up period (Figure 1). Table 1 summarizes the groups' baseline demographic and clinical measures. The two groups had similar age, sex, body mass index (BMI), hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, and HF medications.

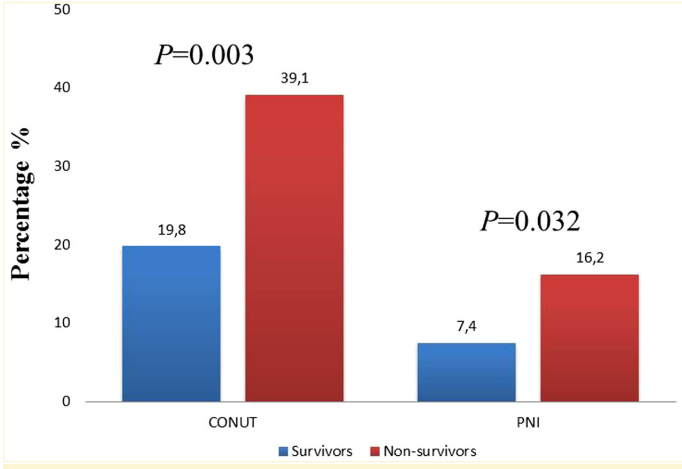

Figure 2. Prevalence of malnutrition defined by CONUT score or PNI higher in the non-survivors.
CONUT, Controlling nutritional status; PNI, Prognostic nutritional index.

Table 1. Demographic, clinical, echocardiographic, and hemodynamic characteristics of patients (survivors and non-survivors)

Variable	Survivors (n = 121)	Non-survivors (n = 74)	*P*
Age (years)	46.0 (37.5–55.0)	48.0 (36.0–55.5)	.651
Follow-up time (day)	965 (635–1276)	273 (92–808)	<.013
Males (n, %)	101 (83.5)	57 (77.0)	
BMI (kg/m^2)	25.9 (22.6–28.9)	24.7 (21.6–28.2)	.177
Comorbidities (n, %)			
Hypertension	21 (17.3)	12 (16.2)	.834
Diabetes	16 (13.2)	8 (10.8)	.763
Hyperlipidemia	4 (3.3)	1 (1.4)	.408
Smoking	38 (31.4)	20 (27.0)	.521
Atrial fibrillation	15 (12.3)	12 (16.2)	.450
NYHA (n, %)			
II	50 (41.3)	10 (13,5)	
III	59 (48.8)	48 (64.8)	.033
IV	12 (9.9)	16 (21.6)	
Hemoglobin (g/dL)	13.9 (12.4–15.5)	13.3 (11.8 15.5)	.081
Platelet (per cubic mm^3)	224.0 (183.0–274.0)	225 (179.0–279.0)	.987
Lymphocyte (x10^3/μL)	1865.0 (1400.0– 2225.0)	1650.0 (1178.0–2000.0)	.002
Creatinine (mg/dL)	0.92 (0.75–1.08)	0.90 (0.79 1.15)	.775
Sodium (mEq/L)	138.0 (134.0–140.0)	136.0 (134.0–138.0)	.031
Potassium (mEq/L)	4.40 (4.0 4.7)	4.3 (3.9–4.6)	.387
Albumin (mg/Dl)	4.1 (3.8–4.4)	4.0 (3.5–4.4)	.176
NT-Pro-BNP (pg mL)	1833.0 (695.0–4837.0)	2170.0 (1134.0–4748.0)	.219
Glucose (mg/dL)	104.0 (92.0–126.0)	106.0 (94.0–124.0)	.931
Total cholesterol (mg/dL)	176.0 (136.0–213.0)	168.0 (118.0–205.0)	.178
HF medications (n, %)			
Beta blocker	91 (75.2)	53 (71.6)	.075
ACEI, ARB or ARNI	94(77.6)	56(75.7)	.758
Spironolactone	90 (74.3)	58 (78.3)	.084
Diuretic	97 (80.1)	62 (83.7)	.644
Ivabradin	32 (26.4)	18 (24.3)	.135
Digoxin	34 (28.0)	21 (28.3)	.869
Echocardiography			
LVEF (%)	79 (65.3)	48 (64.9)	.950
Severe MR (n, %)	29 (23.9)	23 (31.0)	.271
Severe TR (n, %)	92 (76.0)	55 (75.3)	.933
TAPSE (cm)	1.6 (1.3–1.9)	1.4 (1.1– 1.8)	.041
Right heart catheterization			
CO (L/min)	3.4 (2.87–3.9)	3.3 (2.6–3.8)	.074
PAWP (mm Hg)	22.0 (17.0–28.0)	23.0 (18.0–29.0)	.505
PAPm (mm Hg)	30.0 (20.0–40.0)	34.0 (26.0–42.0)	.022
RAP (mm Hg)	9.0 (6.0–14.0)	10.0 (6.0–15.0)	.304
PVR (WU)	2.1 (1–4.4)	3.4 (1.3–5.2)	.041

Values are presented as mean ± SD, percent of cohort, and median (25th–75th percentile).
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CO, cardiac output; LVDD, left ventricle diastolic dysfunction; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; NT Pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAPm, pulmonary artery mean pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, Tricuspid regurgitation.

Table 2. Baseline characteristics for continuous and categorical malnutrition variables

Variable	Survivors (n = 121)	Non-survivors (n=74)	
Continuous variable			***P* value for continuous[a]**
CONUT score (median, IQR)	0 (0–1)	1 (0–2)	.051
PNI score (median, IQR)	50 (45.6–55)	48 (43.6–53.3)	.055
Categorical variable			***P* value for categorical[b]**
CONUT-defined malnutrition (n, %)	24 (19.8)	29 (39.2)	.003
PNI-defined malnutrition (n, %)	9 (7.4)	12 (16.2)	.032

[a]Mann-Whitney U test was used for continuous variables. [b]Chi-squared test was used for categorical variables
CONUT, Controlling nutritional status; PNI, prognostic nutritional index; IQR, interquartile range.

Compared to the survivors, non-survivors had a higher rate of NYHA class III and IV and a lower rate of NYHA class II (*P* = .03). Serum hemoglobin, platelet count, creatinine, potassium, albumin, NT pro-BNP, glucose, and total cholesterol were identical in the two groups in the laboratory; however, lymphocyte count and sodium levels were lower in the non-survivors (*P* = .002 and *P* = .03, respectively). In the echocardiographic findings, LVEF, the presence of severe mitral regurgitation, and severe tricuspid regurgitation were similar between the two groups, and tricuspid annular plane systolic excursion was lower in non-survivors (*P* = .04). The non-survivors had higher PAPm and PVR (*P* = .02 and *P* = .04, respectively) as well as comparable CO, PAWP, and RAP than those of the survivors.

Table 2 shows the baseline characteristics of the two groups for continuous and categorical malnutrition variables. The survivors and non-survivors had similar median CONUT and PNI risk scores (0 [0–1], *P* =.05 and 48.2 [43.6–53.3], *P* = .05, respectively).

Table 3. Univariate Cox regression analysis of confounder variables for mortality

Variables	Unadjusted HR (95% CI)	*P*
Age (37–55 years)	1.00 (0.70–1.43)	.974
NYHA (II–IV)	2.03 (1.02–4.04)	.042
AF	1.38 (0.74–2.56)	.319
LVEF (15–20)	0.80 (0.59–1.08)	.144
Severe MR	1.24 (0.76–2.83)	.385
Severe TR	0.98 (0.58–1.66)	.952
Hb (12.1–14.7)	0.68 (0.50–0.94)	.026
Na (134–140)	0.66 (0.46–0.94)	.023
NTpro-BNP (866–4755)	1.10 (0.93–1.30)	.565
PAPm (22–41)	1.69 (1.17–2.42)	.004
PVR (1–4.85)	1.4 (1.04–2.03)	.022
RAP (6–14)	1.3 (0.97–1.75)	.075
CO (2.7–3.8)	0.68 (0.49–0.93)	.001
CONUT continuous (0–2)	1.41 (1.11–1.79)	.004
CONUT-defined malnutrition	2.48 (1.55–3.97)	<.001
PNI continuous (45.5–54.5)	0.78 (0.64– 0.95)	.014
PNI-defined malnutrition	1.97 (1.01–3.86)	.042

AF, atrial fibrillation; NTpro-BNP, N-terminal pro-brain natriuretic peptide; CO, cardiac output; CONUT, controlling nutritional status score; Hb, hemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; Na, sodium; NYHA, New York Heart Association; PAPm, pulmonary artery mean pressure; PNI, prognostic nutritional index; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TR, Tricuspid regurgitation.

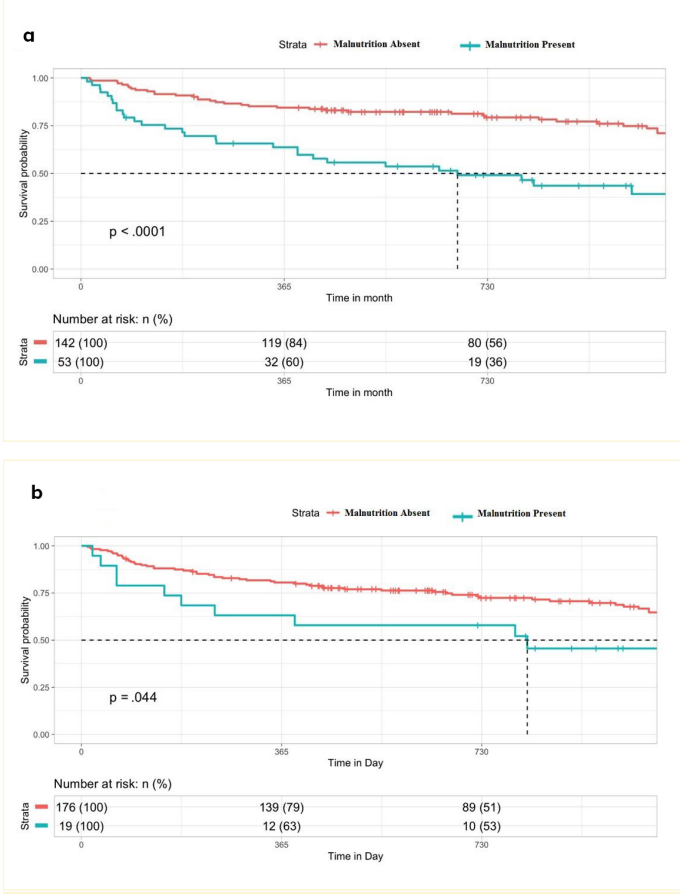

Figure 3. Malnourished patients have lower survival. (A) CONUT score, (B) PNI score.
CONUT, controlling nutritional status; PNI, prognostic nutritional index.

Table 4. Adjusted Cox regression model for continuous and categorical malnutrition scores

Variables	Hazard ratio and CI	*P*	Likelihood chi-squared	R^2
Model-1 CONUT				
CONUT continuous (from 0 to 2)	1.63 (0.84–3.17)	.121	15.02	0.08
CONUT categorical Malnutrition present	1.92 (1.12–3.27)	.014	18.22	0.10
Model-2 PNI				
PNI continuous (from 45.5 to 54.5)	0.83 (0.64–1.08)	.175	14.36	0.08
PNI categorical				
Malnutrition present	1.64 (0.80–3.40)	.184	14.28	0.08

Two models were adjusted with such variables as age, NYHA class, sodium, hemoglobin, PAPm, PVR, and CO.
CI, confidence interval, CO, cardiac output; CONUT, controlling nutritional status score; NYHA, New York Heart Association; PAPm, pulmonary artery mean pressure; PVR, pulmonary vascular resistance; PNI, prognostic nutritional index.

Table 5. Correlation of PNI and CONUT score with demographic, echocardiographic, and hemodynamic parameters

	PNI		CONUT	
Variables	Correlation coefficient (r:)	*P*	Multivariate OR, 95% CI	*P*
PNI			−0.80	< .001
CONUT	−0.80	<.001		
Age	−0.022	.751	0.025	.721
BMI	−0.075	.291	0.125	.079
LVEF	0.163	.022	−0.174	.014
CO	0.117	.101	−0.024	.730
PAPm	−0.142	.047	0.098	.170

BMI, body mass index; CO, cardiac output; CONUT, controlling nutritional status score; LVEF, left ventricular ejection fraction; PAPm, pulmonary artery mean pressure; PNI, Prognostic nutritional index.

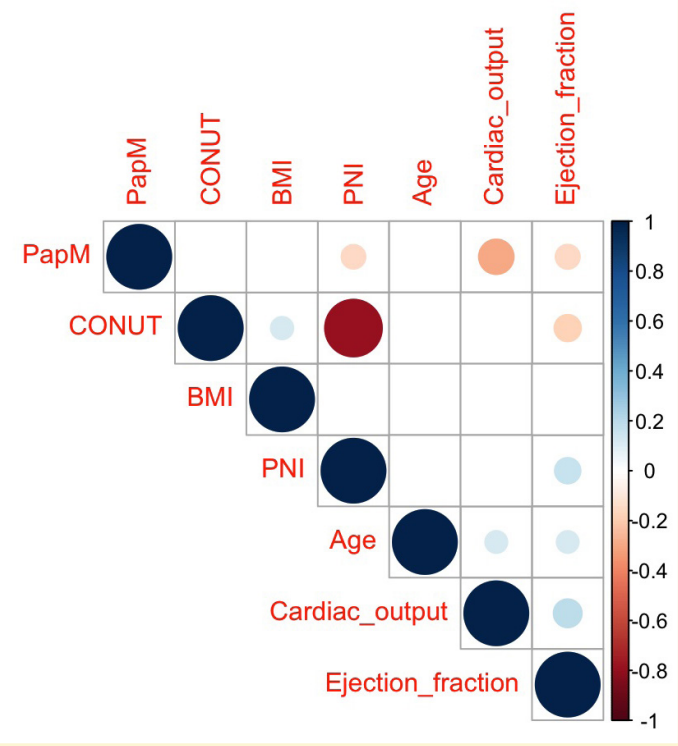

Figure 4. Correlation of PNI and CONUT score with demographic, echocardiographic and hemodynamic parameters. Dark blue demonstrates strong positive correlation, dark red demonstrates strong negative correlation.
BMI, body mass index; CO, cardiac output; CONUT, controlling nutritional status score; LVEF, left ventricular ejection fraction; PAPm, pulmonary artery mean pressure; PNI, prognostic nutritional index.

CONUT-defined malnutrition and PNI-defined malnutrition were found to be higher in non-survivors than in survivors (39.2% and 19.8%, *P* = .003 and 16.2% versus 7.4%, *P* = .032), Table 2 and Figure 2.

Two different Kaplan-Meier curves with log-rank tests were performed based on the CONUT and PNI scores, Figures 3A and 3B.

We demonstrated a higher risk of death in patients with malnutrition than in patients without malnutrition, as defined by CONUT and PNI. The univariate regression analysis showed that NYHA class (from II to IV) (HR: 2.03, 95% CI: 1.02–4.04, *P* = .04), sodium (from 134 to 140) (HR: 0.66, 95% CI: 0.46–0.94, *P* = .02), hemoglobin (from 12.1 to 14.7) (HR: 0.68, 95% CI: 0.50–0.94, *P* = .02), PAPm (from 22 to 41) (HR: 1.69, 95% CI: 1.17–2.42, *P* = .004), PVR (from 1 to 4.85) (HR: 1.4, 95% CI: 1.04–2.03, *P* = .02), CO (from 2.7 to 3.8) (HR: 0.68, 95% CI: 0.49–0.93, *P* = .001), CONUT score (from 0 to 2) (HR: 1.41, 95% CI:1.11–1.79, *P* = .004), PNI score (from 45.5 to 54.5) (HR: 0.78, 95% CI: 0.64–0.95, *P* = .01), CONUT-defined malnutrition (HR: 2.48, 95% CI: 1.55–3.97, *P* < 0.001), and PNI-defined malnutrition (HR: 1.97, 95% CI: 1.01–3.86, *P* = .04) were the predictors of mortality. Other variables are presented in Table 3.

The predictors that were significant in the univariate analysis were modeled in the multivariate analysis. Two different multivariable models were created; Model 1 (for CONUT) and Model 2 (for PNI). Both models were adjusted to such variables as age, NYHA class, sodium, hemoglobin, PAPm, PVR, and CO. We tested for collinearity in the multivariate model using the variance inflation factor. Because the variance inflation factor was lower than 5, we could use PAPm, PVR, and CO in the model. Furthermore, the malnutrition scores that we investigated were included in the models as categorical and continuous variables, respectively. An increase in CONUT score from 0 to 2 (in model 1) and an increase in PNI score from 45.5 to 54.5 (in model 2) were not associated with mortality (HR: 1.63, 95% CI: 0.84–3.17, *P* = .12 and HR: 0.83, 95% CI: 0.64–1.08, *P* = .17, respectively). Although the CONUT-defined malnutrition (in model 1) was an independent predictor of mortality, the PNI-defined malnutrition (in model 2) was not a predictor of mortality (HR: 1.92, 95% CI: 1.12–3.27, *P* = .001 and HR: 1.64, 95% CI: 0.80–3.40, *P* = .18, respectively) (Table 4).

There was a weak positive correlation between PNI score and LVEF (r: 0.163, *P* = .022), a weak negative correlation between PNI score and PAPm (r: −0.142, *P* = .047) and a strong negative correlation between PNI and CONUT score (r: 0.80, *P* < .0001). There was a weak negative correlation between CONUT score and LVEF (r: −0.174, *P* = .014,) (Table 5 and Figure 4).

Discussion

PNI and CONUT scores, which are simple metrics for evaluating malnutrition based on blood albumin levels, lymphocyte count, and cholesterol, were found to predict mortality in candidates listed for HT in this study. These findings highlight the usefulness of a quick assessment technique for determining the nutritional status of these candidates and identifying the need for early intervention in those who are malnourished.

HF is caused by a combination of factors like poor cardiac function, increased neurohumoral mechanisms, and inflammation.[15,16] Drug resistance, electrolyte problems, concomitant infections, and multiorgan dysfunctions are all factors that have been associated with poor prognosis in patients hospitalized for

HF.[17] Moreover, nutritional disorders are frequently seen in these patients. Intestinal edema caused by HF causes problems such as anorexia and malabsorption in patients, causing an acceleration of the catabolic process and an increase in the inflammatory state.[18] In individuals with severe HF, cardiac cachexia is a major manifestation of a catabolic state in which resting metabolic rates rise and gastrointestinal malabsorption prevails. Weight loss occurs as a result of these circumstances, and the prognosis worsens. Fatigue, dyspnea, low daily activity, and muscle weakness are some of the symptoms that patients with weight reduction experience.[19,20] The impact of cardiac cachexia on prognosis in HF patients has recently been studied, and it has emerged as a target in the therapy of HF.[21] Malnutrition causes a variety of issues in patients with HF, and thus it is crucial to assess and treat it. Treatment of malnutrition may aid in lowering the rate of readmission for decompensation and improving prognosis.[21]

The use of BMI alone in the assessment of malnutrition has a low sensitivity for predicting severe malnutrition among cardiac patients and may not confirm the adequacy of energy intake in patients with HF. Therefore, BMI is not an ideal measure of body size and composition in individuals with HF and should not be used as a substitute for nutritional status.[22] Because both systemic inflammation and malnutrition have been linked to cardiovascular events, assessing the immune-nutritional status in patients with cardiovascular diseases has become increasingly important in recent years. In the past decades, objective tools such as the CONUT and PNI scores have been used to assess the immune-nutritional state of patients with various diseases, and multiple studies have reported the effectiveness of these risk scores in predicting mortality in patients with HF.[7,8,23-25]

Assessment of malnutrition by CONUT

The CONUT score, which includes serum albumin, total cholesterol levels, and total lymphocyte count for assessing nutritional status, is an effective method for early detection and continuous monitoring of malnutrition in hospitals. The CONUT score has been shown to have a prognostic impact in patients with severely decompensated acute HFrEF and HF with preserved ejection fraction.[7,8,23,26] Yoshihisa et al[25] found that the CONUT score was superior to those of albumin, total cholesterol, total lymphocyte count, and BMI. Similar to previous studies, we found that the prevalence of CONUT-defined malnutrition was more common (39.2% versus 19.2%) in non-survivors than in survivors (Figure 2). In survival analysis, CONUT-defined malnutrition was associated with lower survival rates in candidates for HT ($P < .001$). We also found that CONUT-defined malnutrition was an independent predictor of mortality. In addition, this study demonstrated that CONUT score had a strong negative correlation with PNI and a weak negative correlation with LVEF. It was not correlated with age, BMI, CO, and PAPm.

Assessment of malnutrition by PNI

PNI has been characterized as a straightforward and objective predictor of postoperative outcomes in patients with cancer.[6,14] Furthermore, studies indicate that PNI is related to a poor prognosis in coronary artery disease and in systemic diseases.[10,11,23] PNI, which is based on serum albumin concentration and total lymphocyte count, might theoretically represent both malabsorption and chronic inflammation in patients with HF. It was revealed to have more prognostic predictive power than its components alone. This was true for both patients with HFrEF and those with HF with a preserved ejection fraction.[7,8,23-25] Cheng et al[24] investigated the impact of PNI in hospitalized patients with acute HF and found that individuals with lower PNI levels had a worse prognosis than those with greater PNI levels at admission. Shirakabe et al[23] examined data from 458 patients to identify predictors of in-hospital mortality and found that PNI and CONUT score could predict in-hospital mortality. As in previous studies, we found that the prevalence of PNI-defined malnutrition and the PNI score was higher in non-survivors than in survivors (16.2% versus 7.4%) (Figure 2). In survival analysis, PNI-defined malnutrition was associated with lower survival rates in candidates for HT ($P < .001$). Although the univariate analysis revealed that the PNI score and the PNI-defined malnutrition were predictors of mortality in candidates for HT; in the adjusted model, they were not independent predictors of mortality from the other confounding risks. In addition, this study demonstrated that PNI had a strong negative correlation with CONUT, a weak positive correlation with LVEF, and a weak negative correlation with PAPm. It was not correlated with age, BMI, and CO.

The prevalence of reported malnutrition varies between studies, which could be owing to changes in the severity of HF or the use of different scoring systems. Malnutrition prevalence, however, varies significantly depending on the method used, ranging from 8% (PNI) to 54% (CONUT) in the same group of patients.[8] Sze et al. demonstrated that the prevalence of malnutrition was higher when malnutrition was estimated by CONUT than when estimated with PNI (54% versus 8%) among outpatients with HF.[8] Similarly, Alataş et al[7] found that CONUT-defined malnutrition (72.0%) was higher than PNI-defined malnutrition (27.7%) in patients with acute decompensated HF. Sze et al[8] attributed the higher frequency of CONUT-defined malnutrition to statin treatment as CONUT contains total cholesterol levels in its formula, which can be impacted by statin treatment. When we examine these two studies, it is observed that the malnutrition rate is higher in patients with acute decompensated heart failure than in those with compensated heart failure. In our cohort, the prevalence of CONUT-defined malnutrition was 27.1% and that of PNI-defined malnutrition was 10.7%. As can be seen, the malnutrition rate in our study (particularly in CONUT-defined malnutrition) was less than in other studies, including patients with acute and chronic HF. We attributed this situation to the following reasons. First, we excluded patients who were taking statins, which could result in a lower CONUT score and rate of CONUT-defined malnutrition; second, patients with cardiogenic shock, intra-aortic balloon pump, and inotropic dependency (these situations may also cause malnutrition) were also excluded from the study because these patients were HT candidates,

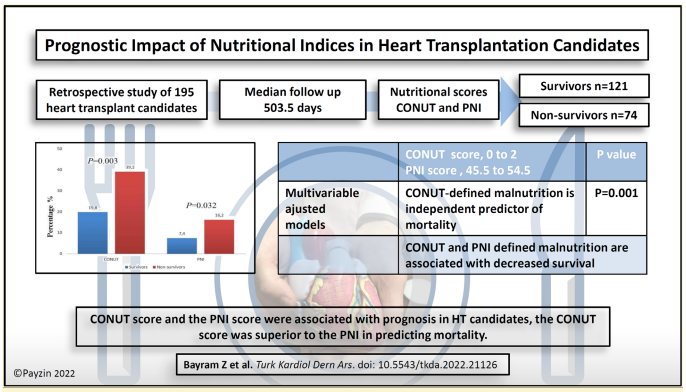

Figure 5. Visual summary of the article

comorbidities causing contraindication to HT, which could also cause malnutrition, were excluded from the study. All of these exclusion criteria may have contributed to our decreased malnutrition rates.

There was no correlation between PNI and age, BMI, and CO, and a weak correlation between PNI and LVEF and PAPm. In addition, there was no correlation between CONUT and age, BMI, CO, and PAPm, and a weak correlation between CONUT and LVEF. Although we figured that the malnutrition score was correlated with parameters that were related to HF severity, we were unable to prove this correlation.

The greatest strength of this study is that it is the first study to investigate the relationship of these nutritional indices with mortality in candidates listed for HT. Many studies did not exclude patients who were on statin therapy. However, statin treatment has an impact on total cholesterol levels, which may reflect either the effects of medication or nutritional status. Consequently, the causal relationships between cholesterol, nutritional status, and medication remained unclear in the previous studies.[23] In our study, we showed that the CONUT score is associated with mortality, even in those who did not receive statin therapy.

Screening for malnutrition in candidates for HT may actually enable the early identification and characterization of individuals at risk of developing cachexia. Treatment of malnutrition may decrease mortality in these candidates and may also decrease mortality after HT. Future studies should focus on whether better use of available treatments might improve nutritional status and eventually survival in candidates for HT.

Limitations

Our study's main limitations were its retrospective and single-center design. In addition, we were unable to rank the severity of malnutrition that is more associated with mortality because the prevalence of malnutrition was lower in our study than in previous studies. We attribute these conditions to the fact that even though our patients had advanced heart failure, the mean age, and comorbidities, which can cause malnutrition, in previous studies were higher than in our study. Second, our study excluded patients with inotropic dependence, extreme comorbidities that cause contraindications to HT, and patients over the age of 70 years. Finally, we did not investigate changes in nutritional status as the clinical situation changed over time.

Conclusion

Mortality markers in patients with HF are constantly being investigated. In our study, we showed that the CONUT score and PNI can be used as mortality markers in patients with ESHF who are evaluated for HT and that the CONUT score was superior to PNI in predicting mortality in these patients. Malnutrition scores, calculated with simple formulas, should be considered as cheap and easily accessible methods that can be used in the follow-up of patients and in determining their prognosis. Although PNI and CONUT were good measures in the assessment of malnutrition in candidates for HT, their correlations with age, BMI, LVEF, CO, and PAPm were absent or weak.

Visual summary of the article can be seen in Figure 5.

Ethics Committee Approval: Ethics committee approval was received for this study from the Kosuyolu Heart Training and Research Hospital (Approval Date: March 9, 2017; Approval Number: 2017.3/9-32).

Informed Consent: Informed consent was not obtained due to the retrospective design of study.

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