Medical Principles and Practice

# **Original Paper**

Med Princ Pract 2022;31:368–375 DOI: 10.1159/000524396 Received: October 25, 2021 Accepted: March 24, 2022 Published online: April 8, 2022

# Poor Nutritional Status Is Associated with Arrhythmic Events on 24-Hour Holter Recording

Ozge Kurmus Ferik<sup>a</sup> Kursat Akbuga<sup>a</sup> Hatice Tolunay<sup>b</sup> Turgay Aslan<sup>a</sup> Murat Eren<sup>a</sup> Aycan Fahri Erkan<sup>a</sup> Berkay Ekici<sup>a</sup> Ebru Akgul Ercan<sup>a</sup> Celal Kervancıoglu<sup>a</sup>

<sup>a</sup>Department of Cardiology, Faculty of Medicine, Ufuk University, Ankara, Turkey; <sup>b</sup>Department of Cardiology, Gulhane Education and Research Hospital, Ankara, Turkey

#### **Highlights of the Study**

- Malnutrition is associated with cardiovascular disease morbidity and mortality.
- It remains unclear whether the adverse outcomes occur because of arrhythmias in malnourished patients.
- Arrhythmias may be the cardiac consequence of malnutrition.

# Keywords

 $\label{eq:cardiology} Cardiology \cdot \mbox{Prognostic nutritional index} \cdot \mbox{CONUT score} \cdot \mbox{Arrhythmia}$ 

# Abstract

**Background:** Malnutrition is associated with cardiovascular disease morbidity and mortality. Arrhythmias may be the cardiac consequences of malnutrition. **Objectives:** The objective of the study was to evaluate the association between prognostic nutritional index (PNI), Controlling Nutritional Status (CONUT) score, and arrhythmic events on 24-h electrocardiography (ECG) Holter recording in patients without manifested arrhythmia. **Methods:** In this retrospective analysis of 477 patients who underwent 24-h ECG Holter monitoring, PNI and CONUT score were calculated and patients were divided into tertiles according to PNI and into three groups according to CONUT score; 0: normal, 1–2: mild risk of malnutrition,  $\geq$ 3: moderate-severe risk of malnutrition. Arrhythmic

Karger@karger.com www.karger.com/mpp © 2022 The Author(s). Published by S. Karger AG, Basel

This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial-4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense), applicable to the online version of the article only. Usage and distribution for commercial purposes requires written permission. events were compared between PNI tertiles and CONUT score groups. Results: Total number of premature atrial contractions, premature ventricular contractions (PVCs), PVC burden, and incidence of paroxysmal atrial fibrillation (PAF) were significantly higher in patients within the lowest PNI tertile. Total number of PVCs, PVC burden, and incidence of PAF were significantly higher in patients with CONUT score  $\geq$ 3. The cut-off value for PNI to predict the presence of PVC was defined as 39.41 using ROC curve analysis. The area under the curve was 0.650 (p < 0.001). Multivariate analysis showed that PNI was independent predictor of the presence of PVC and PAF. Also, CONUT score was independent predictor of the presence of PVC and PAF. Incidence of nonsustained ventricular tachycardia did not differ between PNI tertiles or CONUT score groups. Conclusion: Poor nutritional status, assessed by PNI and CONUT score, is associated with arrhythmic events on 24-h ECG Holter recording in patients without manifested arrhythmia.

© 2022 The Author(s). Published by S. Karger AG, Basel

Correspondence to: Ozge Kurmus Ferik, ozge\_kurmus@yahoo.com

#### Introduction

Malnutrition is reported to be associated with a poor prognosis in patients with heart failure or atherosclerotic cardiovascular disease (CVD) [1, 2]. The prognostic nutritional index (PNI) and Controlling Nutritional Status (CONUT) score are easily calculated and established methods for evaluating the objective nutritional status. Numerous clinical studies have indicated that PNI and CONUT scores are associated with CVD morbidity and mortality in patients with heart failure and myocardial infarction or in patients undergoing percutaneous coronary intervention or coronary artery bypass grafting [3–6]. However, no previous study has exclusively investigated the predictive value of nutritional indices for arrhythmic events. Therefore, we examined the relationship between PNI and CONUT score and arrhythmias on 24-h electrocardiography (ECG) Holter recording in patients without a previous diagnosis of any arrhythmia.

#### Methods

#### Study Population

This study is a retrospective analysis derived from a single center. We analyzed the data of patients who had 24-h ECG Holter recording from consecutive outpatients who applied to our outpatient clinic with complaints of palpitation, irregular heartbeats, and arrhythmia between January 2019 and December 2020. Patients with missing serum albumin, total cholesterol, and total lymphocyte count were excluded from this study. Also excluded were patients with known malignancy, active infectious or inflammatory disease, severe renal or liver insufficiency, electrolyte abnormalities, hypo/hyperthyroidism, left ventricular ejection fraction (LVEF) less than 50% (assessed by echocardiography), moderate or severe valvular heart disease, persistent or permanent atrial fibrillation on baseline ECG, previous diagnosis of arrhythmia, previous ablation for arrhythmia, receiving antiarrhythmic medication (Vaughan Williams classes I, III, and V) from the study. Finally, we evaluated the data of 477 patients in our analysis. All patients had sinus rhythm on their baseline ECG.

Demographic data, laboratory data from fasting venous blood samples, and information about coronary risk factors and medications on admission were retrospectively collected from patient's files and analyzed. The assessed clinical parameters were age, gender, weight, and height and coronary risk factors. Hypertension was defined as systolic blood pressure  $\geq$ 140 mm Hg and/or diastolic blood pressure  $\geq$ 90 mm Hg or current medication with antihypertensive drugs. Patients were defined as diabetic if they had been informed of this diagnosis before and had been using oral antidiabetic drugs or insulin treatment on admission. Coronary artery disease (CAD) was defined as the presence of imaging evidence of  $\geq$ 50% of the diameter in at least one major coronary artery or documentation of myocardial infarction or coronary revascularization. Body mass index (BMI) was calculated as body weight in kilograms divided by the squared value of body height in meters (kg/m<sup>2</sup>).

This study was approved by our institutional review board. Written informed consent was not obtained because the study data were analyzed retrospectively. The research protocol was approved by Mersin University Clinical Research Ethics Committee (Number: 76/2021).

#### Evaluation of Nutritional Indices

The baseline PNI was calculated as  $10 \times \text{serum}$  albumin (g/dL) + 0.005 × total lymphocyte count (per mm<sup>3</sup>) [7]. Baseline CONUT score was calculated from serum albumin levels, total cholesterol levels, and total lymphocyte counts as previously reported [8]. CO-NUT scores range from 0 to 12. A person with normal nutritional status would have a CONUT score of 0, and the higher the score, the worse the nutritional status. Nutritional indices were categorized based on previous studies and defined classifications. Patients were divided into tertiles according to the PNI. Also, patients were classified according to CONUT score as follows: CONUT score of 0 – normal, 1-2 – mild risk of malnutrition,  $\ge 3$  – moderate-severe risk of malnutrition, as described [9].

#### Twenty-Four-Hour ECG Holter Recording

The number of premature atrial contractions (PACs) and premature ventricular contractions (PVCs), PVC burden (%) defined as total number of PVC/total beats, and presence of paroxysmal atrial fibrillation (PAF) and supraventricular tachycardia (SVT) or nonsustained ventricular tachycardia (NSVT) were obtained from the 24-h ECG Holter recording. Three or more consecutive PACs were considered as SVT. NSVT was defined as three or more consecutive regular ventricular beats at a rate of greater than 100 beats/ minute with a duration of less than 30 s. The arrhythmic beats and events on Holter recording were verified by two experienced cardiologists.

#### Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range); categorical variables were defined as percentages. The distribution of continuous variables was considered as normal or not based on the Kolmogorov-Smirnov test. One-way ANOVA or Kruskal-Wallis tests were used to compare continuous variables. Conover-Inman or least significant difference tests were performed for the binary comparisons among the groups. Differences in the distribution of categorical variables were assessed by  $\chi^2$  test. Multiple logistic regression analysis with backward elimination was used to identify independent predictors of PVCs and PAF and was performed separately for PNI and CONUT scores. The selection of variables for the multivariate analysis was based on previous reports and clinical importance. Age, gender, LVEF, BMI, diabetes mellitus, hypertension, CAD, creatinine, the use of  $\beta$ -blockers, and the use of nondihydropyridine calcium channel blockers were included in the analysis as confounding variables. The area under the receiver operating characteristic (ROC) curve was used to indicate the predictive value of PNI for PVC. Pearson's or Spearman's correlation analysis was used to examine correlation between continuous variables. A *p* value of <0.05 was considered statistically significant. Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Clinical and laboratory characteristics of patients stratified by tertiles of the PNI

Variable	Overall	PNI			p value
		tertile 1 ( <i>n</i> = 159)	tertile 2 ( <i>n</i> = 159)	tertile 3 ( <i>n</i> = 159)	
Age	60.0±17.8	67.1±15.5	60.6±16.0	52.6±18.9	<b>&lt;0.001</b> <sup>a, b, c</sup>
Male, %	42.2	42.1	42.1	44	0.926
Hypertension, %	54.4	65.0	51.9	47.1	0.005
Diabetes mellitus, %	21.8	28	22.2	15.5	0.028
CAD, %	24.4	33.8	23.4	16.8	0.002
Smoking, %	19.7	14.6	25.3	20.0	0.061
BMI, kg/m <sup>2</sup>	24.2±2.4	22.9±2.4	24.5±2.8	24.8±3.0	<b>0.025</b> <sup>a, b</sup>
LVEF, %	61.4±6.1	60.1±6.8	62.1±5.3	61.9±6.0	<b>0.005</b> <sup>a, b</sup>
Beta blocker, %	35.7	43.3	30.4	33.5	0.045
Nondihydropyridine calcium channel blockers, %	3.6	1.9	7.0	1.9	0.022
Statin, %	18.2	23.6	15.8	14.8	0.089
CONUT score	1.36±1.2	2.79±2.0	0.71±0.9	0.6±1.0	<0.001 <sup>a, b</sup>
Serum albumin, g/dL	3.87±0.48	3.31±0.32	3.94±0.11	4.37±0.20	<0.001 <sup>a, b, c</sup>
Total cholesterol, mg/dL	196.3±47.0	188.2±48.4	198.7±45.3	200.6±46.5	<b>0.046</b> <sup>b</sup>
LDL cholesterol, mg/dL	123.9±39.0	117.4±35.4	123.0±39.0	129.9±41.5	<b>0.046</b> <sup>b</sup>
HDL cholesterol, mg/dL	49.7±14.9	47.3±15.7	50.8±14.5	50.8±14.8	0.031 <sup>a, b</sup>
Triglyceride, mg/L	141.1±77.3	135.5±69.3	141.2±78.1	145.9±84.6	0.781
Creatinine, mg/dL	1.03±0.5	1.16±1.0	1.02±0.77	0.93±0.75	0.189
White blood cell count, $\times 10^{9}$ /L	7.72±2.3	7.97±2.5	7.64±2.1	7.38±2.0	0.237
Hemoglobin, g/dL	13.9±4.3	12.9±2.5	13.8±2.8	14.6±3.0	<0.001 <sup>a, b, c</sup>
Lymphocyte count, per mm <sup>3</sup>	2.10±0.7	1.87±0.7	2.20±0.7	2.23±0.7	<0.001 <sup>a, b</sup>
Heart rate (mean±SD), bpm	77.10±7.35	77.5±7.42	76.7±7.28	77.07±6.57	0.566
PACs, mean±SD, n	986.7±3045.6	1322.2±3353.9	971.1±3085.1	722.8±2727.9	<0.001 <sup>a, b</sup>
Median (interquartile range)	31 (259)	90 (557)	31 (157)	12 (136)	
PVCs, mean±SD, n	1619.4±4703.3	1743.8±3950.8	1880.4±5616.9	1307.9±4457.2	<b>&lt;0.001</b> <sup>a, b</sup>
Median (interquartile range)	10 (638)	137 (1447)	8.5 (458)	2 (289)	
PVC burden, mean±SD, %	1.66±1.61	1.87±4.12	1.87±5.27	1.33±4.42	0.001 <sup>a, b</sup>
Median (interquartile range)	0.01 (1)	0.31 (1.35)	0.01 (1)	0.01 (0.53)	
NSVT, %	6.9	8.8	8.5	3.8	0.158
PAF, %	9.7	16.2	6.5	7.0	0.006
SVT, %	24.8	34.0	24.0	17.2	0.003

CONUT, Controlling Nutritional Status; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PACs, premature atrial contractions; PAF, paroxysmal atrial fibrillation; PNI, prognostic nutritional index; PVCs, premature ventricular contractions; SVT, supraventricular tachycardia. Significant differences were found between <sup>a</sup> tertile 1 versus tertile 2, <sup>b</sup> tertile 1 versus tertile 3, and <sup>c</sup> tertile 2 versus tertile 3.

# Results

# **Baseline Characteristics**

The mean age of study population was  $60.0 \pm 17.8$  years, and 42.2% of the 477 patients were males. Baseline characteristics are presented in Table 1. Mean LVEF was  $61.4 \pm$ 6.1%, mean PNI was  $38.7 \pm 4.9$ , and mean CONUT score was  $1.36 \pm 1.2$ . The baseline clinical and laboratory characteristics of the study patients according to the PNI tertiles are presented in Table 1. Patients in the lowest PNI tertile were significantly older and had a higher prevalence of hypertension, diabetes mellitus, and history of CAD as well as lower LVEF, hemoglobin, and higher CONUT score. Patients in the lowest PNI tertile more commonly received  $\beta$ -blockers. Total number of PACs, PVCs, and PVC burden were higher in the patients within the lowest PNI tertile. PAF and SVT were more commonly detected on 24-h ECG Holter recording in patients within lowest PNI tertile. The incidence of NSVT did not differ among the groups. The baseline clinical and laboratory characteristics of the study patients according to the CONUT score are presented in Table 2. Patients with higher CONUT scores were significantly older and had higher prevalence of hypertension and history of CAD as well as lower LVEF, PNI, triglyceride, Table 2. Clinical and laboratory characteristics of patients stratified by CONUT score

Variable	CONUT  score = 0 $(N = 204)$	CONUT  score = 1-2 $(N = 175)$	CONUT score $\ge 3$ ( $N = 98$ )	<i>p</i> value
Age	58.0±16.7	58.5±18.8	67.6±16.5	<b>&lt;0.001</b> <sup>b, c</sup>
Male, %	35.3	49.1	46.7	0.117
Hypertension, %	47.3	52.9	74.2	<0.001
Diabetes mellitus, %	19.4	23.3	28.1	0.252
CAD, %	14.4	29.1	38.2	<0.001
Smoking, %	20.9	24.4	11.2	0.042
BMI, kg/m <sup>2</sup>	24.6±3.3	24.6±2.3	23.4±1.3	<b>0.030</b> <sup>b, c</sup>
LVEF, %	62.4±5.3	61.4±5.9	59.1±7.7	<b>0.002</b> <sup>b, c</sup>
Beta blocker, %	31.3	38.4	40.4	0.215
Nondihydropyridine calcium channel blockers, %	2.5	4.1	5.6	0.402
Statin, %	11.9	22.1	28.1	<0.001
PNI	41.0±3.2	39.3±4.1	32.5±4.4	<b>&lt;0.001</b> <sup>a, b, c</sup>
Serum albumin, g/dL	4.03±0.42	3.91±0.42	3.1±0.53	<b>&lt;0.001</b> <sup>a, b, c</sup>
Total cholesterol, mg/dL	225.2±34.7	176.6±41.9	167.5±44.0	<b>&lt;0.001</b> <sup>a, b</sup>
LDL cholesterol, mg/dL	146.3±32.2	106.7±35.2	103.9±32.2	<b>&lt;0.001</b> <sup>a, b</sup>
HDL cholesterol, mg/dL	51.9±15.8	49.2±14.2	45.7±13.9	<b>0.006</b> <sup>b</sup>
Triglyceride, mg/dL	160.9±90.3	126.6±66.6	123.5±50.3	<b>&lt;0.001</b> <sup>a, b</sup>
Creatinine, mg/dL	0.92±0.6	1.04±0.74	1.29±0.9	<b>0.007</b> <sup>a, b</sup>
White blood cell count, ×10 <sup>9</sup> /L	7.45±2.5	7.76±2.3	8.19±4.2	0.685
Hemoglobin, g/dL	14.0±1.5	14.4±6.5	12.7±3.1	<b>&lt;0.001</b> <sup>b, c</sup>
Lymphocyte count	2.42±0.7	2.03±0.7	1.52±0.7	<b>&lt;0.001</b> <sup>a, b, c</sup>
Heart rate (mean±SD), bpm	76.99±7.11	76.45±7.42	77.84±6.35	0.379
PACs, mean $\pm$ SD, $n$	638.2±2,322.6	1,075.2±2,944.8	1,562.6±4,080.7	<b>&lt;0.001</b> <sup>a, b</sup>
Median (interguartile range)	17 (127)	37 (377)	108 (1,012)	
PVCs, mean $\pm$ SD, n	1,422.2±5,055.8	1,826.0±4,814.9	1,802.5±3,813.9	<b>&lt;0.001</b> <sup>b, c</sup>
Median (interquartile range)	1 (276)	11 (728)	179.5 (1,963)	
PVC burden, mean ± SD, %	1.43±4.8	1.84±4.6	1.97±4.2	<b>&lt;0.001</b> <sup>b, c</sup>
Median (interquartile range)	0 (0.48)	0.01 (1)	1 (2.1)	
NSVT, %	3.5	8.4	12.3	0.158
PAF, %	8.4	6.6	20.7	<0.001
SVT, %	21.8	23.4	34.6	0.070

Abbreviations as in Table 1. Significant differences were found between <sup>a</sup> CONUT score = 0 versus CONUT score = 1-2, <sup>b</sup> CONUT score = 0 versus CONUT score  $\geq 3$ , and <sup>c</sup> CONUT score = 1-2 versus CONUT score  $\geq 3$ .

hemoglobin, and higher creatinine. The use of  $\beta$ -blockers and nondihydropyridine calcium channel blockers did not differ among the three groups. Patients with higher CO-NUT scores more commonly received statins. Total number of PACs was lowest in the patients with CONUT score 0. Total number of PVCs and PVC burden were highest in patients with CONUT score  $\geq 3$ . PAF was more commonly detected on 24-h ECG Holter recording in patients with higher CONUT scores. The incidence of SVT and NSVT did not differ among the groups. The use of statin affects serum total cholesterol, and total cholesterol is a component of CONUT score. So, we excluded the patients receiving statins (18.2%) and reanalyzed the data of patients not receiving statins. Patients with higher CONUT score more commonly had hypertension, PAF, and SVT (p = 0.012, p = 0.010, and p = 0.035, respectively). Total number of PVCs and PVC burden were highest in the patients with highest CONUT scores (p < 0.001, p = 0.005, and p < 0.001, respectively). Total number of PACs was lowest in the patients with CONUT score 0. The incidence of NSVT did not differ among the groups (p = 0.171).

# *Correlations between PNI, CONUT Score, and Arrhythmic Events*

PNI was strongly and negatively correlated with CO-NUT score (r = -0.767, p < 0.001). The number of PVCs positively correlated with number of PACs (r = 0.260, p < 0.001). Correlations between PNI and number of PACs (r = -0.244, p < 0.001), number of PVCs (r = -0.335, p < 0.001), and PVC burden (r = -0.342, p < 0.001) were sig-

Table 3. Multivariate analysis including PNI

	Odds ratio	95% confidence interval	<i>p</i> value
Predictors of PVCs			
PNI	0.936	0.891-0.984	0.009
Age	1.033	1.019-1.047	<0.001
LVEF	0.873	0.825-0.924	<0.001
Predictors of PAF			
PNI	0.911	0.853-0.973	0.005
LVEF	0.904	0.858-0.954	<0.001
CAD	1.267	1.106-1.671	0.005

Table 4. Multivariate analysis including CONUT score

	Odds ratio	95% confidence interval	<i>p</i> value
Predictors of PVCs			
CONUT score	1.177	1.010-1.372	0.037
Age	1.037	1.023-1.051	<0.001
LVEF	0.881	0.833-0.932	<0.001
Predictors of PAF			
CONUT score	1.210	1.016-1.440	0.032
Age	1.041	1.016-1.066	<0.001
LVEF	0.908	0.861-0.957	<0.001
CAD	1.279	1.109–1.714	0.008

nificant. Correlations between CONUT score and number of PACs (r = 0.215, p < 0.001), number of PVCs (r = -0.206, p < 0.001), and PVC burden (r = -0.220, p < 0.001) were significant.

# Multivariate and ROC Analyses

Multivariate analysis revealed PNI as an independent predictor of the presence of PVC (OR = 0.936, 95% CI: 0.891–0.984, p = 0.009) and PAF (OR = 0.911, 95% CI: 0.853–0.973, p = 0.005) (Table 3). Also, multivariate analysis revealed CONUT score as an independent predictor of the presence of PVC (OR = 1.177, 95% CI: 1.010–1.372, p = 0.037) and PAF (OR = 1.210, 95% CI: 1.016–1.440, p = 0.032) (Table 4). The ROC curve of the PNI as a marker to predict the presence of PVC is illustrated in Figure 1. The cut-off value was 39.41 as identified by ROC. The area under the curve of the PNI for predicting the presence of PVC was 0.650 (95% CI: 0.599–0.701, p < 0.001). A PNI value of 39.41 had a sensitivity of 62% and specificity of 66.5%.



**Fig. 1.** Receiver operating characteristic curve of prognostic nutritional index for predicting presence of premature ventricular contraction.

# Discussion

The present study showed that low PNI and high CO-NUT score were significantly associated with frequent PACs, frequent PVCs, and PAF detected on 24-h ECG Holter recording in patients without manifested arrhythmia. To the best of our knowledge, this is the first study to evaluate relationship between nutritional status, estimated by PNI and CONUT score, and arrhythmic events on 24-h ECG Holter recording. The findings of this study suggest that evaluation of nutritional risk may be important for predicting arrhythmic events in patients without manifested arrhythmia. The PNI and CONUT score were demonstrated to be objective and simple tools for assessment of nutritional status [7, 8]. Subsequently, a number of clinical studies were conducted to evaluate the association of the PNI and CONUT score with CVD morbidity and mortality in many patient cohorts. The PNI and CO-NUT score have been shown to predict adverse outcomes in patients with acute and chronic heart failure [1, 3, 10]. Also, PNI and CONUT score were found to be independent predictors of adverse outcomes in patients with CAD [4, 9, 11, 12]. Whether the adverse outcomes in these study cohorts are related to arrhythmias is still unclear.

Malnutrition is commonly prevalent in patients with several CVDs [1, 13, 14]. So far, however, not many studies have evaluated the relationship between nutritional indices, malnutrition, and arrhythmia. More data have recently been provided on the relationship between atrial fibrillation and nutritional indices. Zhu et al. [15] reported that poor nutritional status assessed by CO-NUT score is associated with recurrence of AF following ablation. In older patients with nonvalvular AF, moderate to severe malnutrition assessed by CONUT score and PNI was found to be significantly associated with adverse outcomes including thromboembolic events and death [14]. In previous studies using BMI as a tool to estimate nutritional status, being underweight was reported to be a risk factor for developing AF [16, 17]. In our study, incidence of PAF detected on 24-h ECG Holter recording was higher in those with lower PNI and higher CONUT score compared with patients with higher PNI and lower CONUT score. The main differences in our study are using simple, validated tools for estimating nutritional status, and study population consists of younger, ambulatory patients without manifested arrhythmia. In a meta-analysis including 198,000 patients without history of AF, PACs on 24-48-h ECG Holter recording were significantly associated with AF, first stroke, and mortality [18]. In our study, number of PACs and incidence of PAF were higher in patients with poor nutritional status.

Studies evaluating the relationship between malnutrition and arrhythmias are scarce. Even fewer studies have focused on the impact of malnutrition on arrhythmias other than AF. Malnutrition represented as low geriatric nutritional risk score was significantly associated with mortality in patients who underwent pacemaker implantation for bradycardia [19]. Recently, the relationship between BMI and ventricular arrhythmia has been studied. In a study including patients with implantable cardioverter-defibrillator and ischemic cardiomyopathy, patients with normal BMI compared to overweight and obese patients were found to have more recurrent ventricular arrhythmias and higher mortality [20]. But underweight patients were not included in this study. In a small study including hospitalized patients, malnourished patients (BMI <18.5) had longer QTc interval on ECG than nonmalnourished patients [21]. In patients with cardioverter-defibrillator, the frequency of arrhythmic events was significantly increased and the incidence of ventricular tachycardia/ventricular fibrillation was markedly higher in patients with stage IV cancer than in patients with earlier stages [22]. Cancer is a

Although there is increasing evidence on the relationship between malnutrition and arrhythmias, there is no clear explanation for the underlying pathophysiology. One possible mechanism for this relationship is inflammation, as malnutrition is associated with chronic inflammation and studies have suggested that there is a relationship between inflammation and arrhythmias [23-25]. Other possible mechanisms that may explain the increased risk of having arrhythmic event in the presence of malnutrition are electrolyte imbalance and deficiency of trace elements and vitamins [26]. Endothelial dysfunction is present in patients with arrhythmias and is associated with adverse outcomes, and malnutrition has been shown to be associated with endothelial dysfunction [27, 28]. It has been reported that malnutrition affects cardiac autonomic system in children and some studies in animals have suggested that protein malnutrition causes changes in renin-angiotensin system and sympathetic activity [29-31]. These changes may cause formation of an arrhythmia substrate or predisposition to arrhythmias.

This study has several limitations. One important limitation is that approximately 9 months of the study included the period of the COVID-19 pandemic. During this period, the increased stress and anxiety levels of the patients and changing lifestyles may have triggered changes in their nutritional status and development of possible arrhythmias. Effects of all potential confounding factors on arrhythmia cannot be controlled because of the retrospective design of the study. Also, there is the possibility of bias for nutritional indices from unmeasured confounders such as dietary habits or undiagnosed systemic illness. The observational nature of this study did not allow us to make a cause-and-effect explanation for the nutritional status that was associated with arrhythmic events. There is known daily variability in PAC and PVC frequency, and this might have affected the findings of our study. Further studies are needed to validate the clinical application of nutritional indices in the diagnosis and management of arrhythmias.

well-known risk factor for malnutrition, and there may be a link between malnutrition and ventricular arrhythmias in cancer patients, but we can only speculate about this link based on this study because of the lack of data on the nutritional status of participants. In our study, although the number of PVCs was higher in patients with poor nutritional status than in patients with better nutritional status, incidence of NSVT did not differ between groups.

## Conclusions

In our study, poor nutritional status, represented by low PNI and high CONUT score, was found to be associated with PACs, PVCs, and PAF on 24-h ECG Holter recording in patients without manifested arrhythmia. No single nutritional index to date has been integrated into routine cardiology practice, and findings of our study suggest that nutritional indices might be useful for predicting arrhythmic events.

## **Statement of Ethics**

The research protocol was approved by the Mersin University Clinical Research Ethics Committee: Reference number: 76/2021.

## **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

## **Funding Sources**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## **Author Contributions**

Concept – Ozge Kurmus Ferik; design – Ozge Kurmus Ferik, Kursat Akbuga, Hatice Tolunay, and Turgay Aslan; supervision – Murat Eren, Aycan Fahri Erkan, and Berkay Ekici; materials – Ozge Kurmus Ferik, Aycan Fahri Erkan, Ebru Akgul Ercan, and Celal Kervancioglu; data collection and processing – Ozge Kurmus Ferik, Kursat Akbuga, Turgay Aslan, and Murat Eren; analysis and interpretation – Ozge Kurmus Ferik, Berkay Ekici, Murat Eren, and Hatice Tolunay; literature search – Ozge Kurmus Ferik; writing – Ozge Kurmus Ferik; critical review – Ebru Akgul Ercan, Celal Kervancioglu, and Hatice Tolunay.

## **Data Availability Statement**

Derived data supporting the findings of this study are available from the corresponding author Ozge Kurmus Ferik on request.

## References

- 1 Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, 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;6:476–86.
- 2 Huang BT, Peng Y, Liu W, Zhang C, Chai H, Huang FY, et al. Nutritional state predicts allcause death independent of comorbidities in geriatric patients with coronary artery disease. J Nutr Health Aging. 2016;20:199–204.
- 3 Cheng YL, Sung SH, Cheng HM, Hsu PF, Guo CY, Yu WC, et al. Prognostic nutritional index and the risk of mortality in patients with acute heart failure. J Am Heart Assoc. 2017;6: e004876.
- 4 Chen QJ, Qu HJ, Li DZ, Li XM, Zhu JJ, Xiang Y, et al. Prognostic nutritional index predicts clinical outcome in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Sci Rep. 2017;7:3285.
- 5 Wada H, Dohi T, Miyauchi K, Endo H, Tsuboi S, Ogita M, et al. Combined effect of nutritional status on long-term outcomes in patients with coronary artery disease undergoing percutaneous coronary intervention. Heart Vessels. 2018;33:1445–52.
- 6 Keskin M, İpek G, Aldağ M, Altay S, Hayıroğlu Mİ, Börklü EB, et al. Effect of nutritional status on mortality in patients undergoing coronary artery bypass grafting. Nutrition. 2018; 48:82–6.

- 7 Nodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi. 1984;85:1001–5.
- 8 Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp. 2005;20:38–45.
- 9 Basta G, Chatzianagnostou K, Paradossi U, Botto N, Del Turco S, Taddei A, et al. The prognostic impact of objective nutritional indices in elderly patients with ST-elevation myocardial infarction undergoing primary coronary intervention. Int J Cardiol. 2016; 221:987–92.
- 10 Narumi T, Arimoto T, Funayama A, Kadowaki S, Otaki Y, Nishiyama S, et al. Prognostic importance of objective nutritional indexes in patients with chronic heart failure. J Cardiol. 2013;62:307–13.
- 11 Wada H, Dohi T, Miyauchi K, Jun S, Endo H, Doi S, et al. Relationship between the prognostic nutritional index and long-term clinical outcomes in patients with stable coronary artery disease. J Cardiol. 2018;72:155–61.
- 12 Wada H, Dohi T, Miyauchi K, Doi S, Konishi H, Naito R, et al. Prognostic impact of nutritional status assessed by the controlling nutritional status score in patients with stable coronary artery disease undergoing percutaneous coronary intervention. Clin Res Cardiol. 2017;106:875–83.

- 13 Bonilla-Palomas JL, Gámez-López AL, Anguita-Sánchez MP, Castillo-Domínguez JC, García-Fuertes D, Crespin-Crespin M, et al. Impact of malnutrition on long-term mortality in hospitalized patients with heart failure. Rev Esp Cardiol. 2011;64:752–8.
- 14 Cheng N, Dang A, Lv N, He Y, Wang X. Malnutrition status in patients of very advanced age with nonvalvular atrial fibrillation and its impact on clinical outcomes. Nutr Metab Cardiovasc Dis. 2019;29:1101–9.
- 15 Zhu S, Zhao H, Zheng M, Peng J. The impact of malnutrition on atrial fibrillation recurrence post ablation. Nutr Metab Cardiovasc Dis. 2021;31(3):834-40.
- 16 Sun X, Boyce SW, Hill PC, Bafi AS, Xue Z, Lindsay J, et al. Association of body mass index with new-onset atrial fibrillation after coronary artery bypass grafting operations. Ann Thorac Surg. 2011;91:1852–8.
- 17 Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ, et al. Underweight is a risk factor for atrial fibrillation: a Nationwide Population-Based Study. Int J Cardiol. 2016;215: 449–56.
- 18 Himmelreich JCL, Lucassen WAM, Heugen M, Bossuyt PMM, Tan HL, Harskamp RE, et al. Frequent premature atrial contractions are associated with atrial fibrillation, brain is-chaemia, and mortality: a systematic review and meta-analysis. Europace. 2019;21:698–707.

- 19 Yamaguchi T, Nozato T, Miwa N, Sagawa Y, Watanabe K, Nagata Y, et al. Impact of the preprocedural nutrition status on the clinical outcomes of patients after pacemaker implantation for bradycardia. J Cardiol. 2019;74: 284–9.
- 20 Samanta R, Narayan A, Pouliopoulos J, Kovoor P, Thiagalingam A. Influence of body mass index on recurrence of ventricular arrhythmia, mortality in defibrillator recipients with ischaemic cardiomyopathy. Heart Lung Circ. 2020;29:254–61.
- 21 Cunha DF, Cunha SF, Ferreira TP, Sawan ZT, Rodrigues LS, Prata SP, et al. Prolonged QTc intervals on the electrocardiograms of hospitalized malnourished adults. Nutrition. 2001; 17:370–2.
- 22 Enriquez A, Biagi J, Redfearn D, Boles U, Kamel D, Ali FS, et al. Increased incidence of ventricular arrhythmias in patients with advanced cancer and implantable cardioverterdefibrillators. JACC Clin Electrophysiol. 2017;3:50–6.

- 23 Stenvinkel P, Heimbürger O, Paultre F, Diczfalusy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999;55:1899–911.
- 24 Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol. 2012; 60:2263–70.
- 25 Blangy H, Sadoul N, Dousset B, Radauceanu A, Fay R, Aliot E, et al. Serum BNP, hs-C-reactive protein, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction. Europace. 2007;9: 724–9.
- 26 Anaszewicz M, Budzyński J. Clinical significance of nutritional status in patients with atrial fibrillation: an overview of current evidence. J Cardiol. 2017;69:719–30.

- 27 Khan AA, Thomas GN, Lip GYH, Shantsila A. Endothelial function in patients with atrial fibrillation. Ann Med. 2020;52:1–11.
- 28 Demir M, Kucuk A, Sezer MT, Altuntas A, Kaya S. Malnutrition-inflammation score and endothelial dysfunction in hemodialysis patients. J Ren Nutr. 2010;20:377–83.
- 29 Barreto GS, Vanderlei FM, Vanderlei LC, Leite ÁJ. Impact of malnutrition on cardiac autonomic modulation in children. J Pediatr. 2016;92:638–44.
- 30 Gomide JM, de Menezes RC, Fernandes LG, Silva FC, Cardoso LM, Miranda PH, et al. Increased activity of the renin-angiotensin and sympathetic nervous systems is required for regulation of the blood pressure in rats fed a low-protein diet. Exp Physiol. 2013;98:57–66.
- 31 Silva FC, de Menezes RC, Chianca DA Jr. The implication of protein malnutrition on cardiovascular control systems in rats. Front Physiol. 2015;6:246.