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Prognostic nutritional index as a novel marker for prediction of prognosis in patients with peripartum cardiomyopathy

Bahar Tekin Tak, MD[a,*], Serkan Cay, MD[a], Hilal Erken Pamukcu, MD[b], Firdevs Aysenur Ekizler, MD[a], Habibe Kafes, MD[a], Elif Hande Ozcan Cetin, MD[a], Nedret Ulvan, MD[a], Ozcan Ozeke, MD[a], Firat Ozcan, MD[a], Serkan Topaloglu, MD[a], Dursun Aras, MD[a]

Abstract

The clinical significance of poor nutritional status in patients with peripartum cardiomyopathy (PPCM) is not clearly understood. Prognostic nutritional index (PNI) is a simple nutritional assessment tool, which was first demonstrated to be valuable in patients with colorectal surgeries. We aimed to investigate the predictive value of PNI in patients with PPCM.

A total of 92 patients diagnosed with PPCM were enrolled in this study. PNI was calculated using the following formula: 10 × serum albumin value (g/dL) + 0.005 × total lymphocyte count. The primary endpoint was defined as composite adverse cardiac events that included cardiac death or hospitalization due to worsening heart failure (HF). Cardiac death, hospitalization due to worsening HF, and persistent left ventricular (LV) systolic dysfunction were evaluated, respectively, as secondary endpoints.

Primary composite endpoint was higher in the lower PNI group. After adjusting for other risk factors, PNI was found to be as an independent predictor of primary composite endpoint (odds ratio 0.805; 95% confidence interval 0.729–0.888; $P < .001$). In addition, PNI was significantly associated with secondary endpoints; persistent LV systolic dysfunction as well as cardiac death.

This study identified nutritional status assessed by the PNI seems to be a novel predictor of adverse cardiovascular outcomes in patients with PPCM.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, AF = atrial fibrillation, ARBs = angiotensin receptor blockers, BMI = body mass index, CAD = coronary artery disease, HF = heart failure, ICD = implantable cardioverter defibrillator, LVEDD = LV end-diastolic diameters, LVEF = left ventricular ejection fraction, LVESD = LV end-systolic diameter, NYHA = New York Heart Association, PNI = prognostic nutritional index, PPCM = peripartum cardiomyopathy, STEMI = ST segment elevation myocardial infarction.

Keywords: peripartum cardiomyopathy, prognosis, prognostic nutritional index

1. Introduction

Peripartum cardiomyopathy (PPCM) is defined as a potentially life-threatening disease that occurs at the end of pregnancy or in the first months of postpartum period.[1] This disease is characterized by an onset of unexplained heart failure (HF) with reduced left ventricular (LV) ejection fraction (EF), usually <45%, presenting towards the end of pregnancy or 6 months after delivery in previously healthy women, where no other identifiable cause of HF is found.[2,3] PPCM is endemic in parts of South Africa and remains to be the major cause of cardiovascular maternal death, but its true incidence is unknown.

The etiology of PPCM remains undefined, but various risk factors such as genetic and hormonal mechanisms, abnormal immune, or hemodynamic response to pregnancy, nutrient deficiency, increased oxidative stress, and inflammation have been identified.[2,4]

Clinical presentation of PPCM is highly heterogeneous and the disease might lead to progressive HF, thromboembolic complications, life-threatening arrhythmias, and even cardiac death.[5,6] Although clinical presentations and outcomes vary substantially, clinical investigations indicated LV recovery (defined as recovery to an left ventricular ejection fraction (LVEF) >50%) with a varying range from 23% to 66%; therefore, it is important to identify early predictors of LV recovery in women with PPCM in order to prevent complications and improve outcome.[7,8] Although nearly all recovery of LV function occurred within six months of diagnosis in some series, delayed recovery of LV function has been reported in other studies.[8] In the literature, there are many studies investigating the predictors for LV recovery in patients with PPCM. Several studies have reported that an increased LV end-diastolic diameters (LVEDD), lower

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[a] Department of Cardiology, University of Health Sciences, Ankara City Hospital, [b] Department of Cardiology, Dışkapı Education and Research Hospital, Health Sciences University, Ankara, Turkey.

[*] Correspondence: Bahar Tekin Tak, Sağlık Bilimleri Üniversitesi, Ankara Şehir Hastanesi, Kardiyoloji Klinigi, Ankara 06100, Turkey (e-mail: tekinbahar@yahoo.com).

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baseline LVEF on the initial echocardiogram, older age, late diagnosis, black race, and elevated inflammation plasma markers predict the adverse outcomes in PPCM patients and a lesser probability of recovery.[6,9,10] However, it is still difficult to predict which patients will have full LV recovery and which will develop chronic HF with persistently reduced LVEF. The management of heart failure (HF) due to PPCM is similar to that of HF due to other causes however new treatment approaches may include bromocriptine, pentoxifylline or other potential therapies that affect the immune system.[11]

Malnutrition, which is associated with decreased immune system function, impaired respiratory function, and poor wound healing, has been shown to be a predictor of outcome in patients with chronic illness, including end-stage renal disease, malignancy, and advanced HF.[12,13]

Although nutritional status examination is more complex, objective, and well-recognized indices such as prognostic nutritional index (PNI) have been developed. PNI, calculated from the serum albumin concentration and total lymphocyte count, is a simple and objective indicator that assesses immunonutritional status of patients.[14] Some studies demonstrated that nutritional status measured by PNI is an independent prognostic factor in patients with various cardiovascular diseases such as acute or chronic HF, ST segment elevation myocardial infarction (STEMI), stable coronary artery disease (CAD).[15–17] However, this association has not been previously assessed in patients with PPCM.

In the present study, we aim to investigate the usefulness of PNI in predicting cardiovascular mortality, hospitalization due to worsening HF and persistent LV systolic dysfunction in patients with PPCM.

2. Material and methods

2.1. Study population

From April 2009 to March 2018, 92 patients diagnosed with PPCM in our tertiary reference center were enrolled in this study. Demographic parameters, laboratory and echocardiographic data of all patients were reviewed from their patients' files, clinical follow-up visits and electronic database. The study protocol was reviewed and approved by the institutional ethics committee in accordance with the Declaration of Helsinki. PPCM was accepted as the occurrence of unexplained HF from the last months of pregnancy up to 5 months after delivery with LVEF $<$ 45% and the absence of identifiable heart disease before the last month of pregnancy. All patients were older than 18 years. Patients with any previous congenital or significant organic valvular heart disease and history of cardiomyopathy and coronary heart disease ($\geq$50% luminal stenosis in at least one major coronary artery and their branches) were excluded from this study. A total of 92 patients who met the criteria were included in this study. The follow-up duration was at least 12 months after diagnosis for all patients. They had undergone two-dimensional and M-mode echocardiography with continuous, pulsed and color Doppler imaging at the time of diagnosis and the last follow-up visit with the Vivid 7 system (GE Healthcare, Wauwatosa, WI). EF was calculated by using modified Simpson method. Recovery of LV systolic function was defined as the presence of LVEF $>$ 45%. Echocardiographic parameters, including LVEF, LVEDD, and LV end-systolic diameter (LVESD) were recorded for statistical analysis. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Patients were considered to have hypertension if their blood pressure was $\geq$140/90 mm Hg or if they were taking any anti-hypertensive medication. Diabetes mellitus was defined as fasting blood glucose level of 126 mg/dL or greater and treatment with anti-diabetic medications. Peripheral venous blood was drawn from the antecubital vein and was obtained in the morning after a 12-hour fast. All biochemical analyses were determined using standard methods. PNI was calculated using the following formula: $10 \times$ serum albumin value (g/dL) $+ 0.005 \times$ total lymphocyte count in the peripheral blood (per mm^3). Patients were divided into two groups according to their admission PNI.

All patients were given standard treatment for HF, including diuretics, beta blockers, digitalis, and angiotensin-converting enzyme inhibitors (ACEI). None of the women received bromocriptine treatment.

2.2. Study endpoint

The primary endpoint was defined as composite adverse cardiac events that included cardiac death or hospitalization due to worsening HF. Cardiac death, hospitalization due to worsening HF, and persistent LV systolic dysfunction were evaluated, respectively, as secondary endpoints.

2.3. Statistical analysis

Statistical analysis was performed using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Inc., IL). Continuous variables were presented as mean $\pm$ SD and median with interquartile ranges of appropriate and categorical variables as frequency and percentage. Kolmogorov–Smirnov test was used to test normality of distribution. Differences between groups were evaluated by using Students t test for normally distributed variables and Mann–Whitney U test for variables without normal distribution. The Chi-square or Fisher exact test was used to compare categorical variables as appropriate. Univariate analysis and multivariate analysis with Cox proportional hazards regression was used to evaluate the association between PNI and development of adverse outcomes of PPCMP.

To assess the effects of parameters that were found significant in univariate analysis ($P < .05$) then we used multivariate analysis. In addition, we assessed the collinearity of LVEDD, LVESD, and LVEF before conducting multivariate analysis. Survival estimates were calculated by the Kaplan–Meier method and the log-rank test was used for comparison. Receiver operating characteristic curve (ROC) analysis was used to determine the optimum cut-off levels of PNI value to predict primary endpoint. A P-value $< .05$ (using a two-sided test) was considered significant.

3. Results

3.1. Patient demographics

A total of 92 patients diagnosed with PPCM were enrolled in our study. Baseline clinical, demographic, and echocardiographic characteristics of the study population were described in Table 1. The mean age of the study population was 29.9 $\pm$ 6.4 years old; mean BMI was 22.9 $\pm$ 1.5 kg/m^2, and 32.6% of women presented with New York Heart Association (NYHA) functional class III or IV symptoms. Amongst the 92 patients involved in the study,

Table 1

Baseline clinical, echocardiographic, and laboratory characteristics of patients with and without primary endpoint.

Parameters	Study population N = 92	Event (-) N = 57	Event (+) N = 35	*P* value
Age at diagnosis, years	29.9 ± 6.4	29.9 ± 5.6	29.8 ± 7.5	.979[a]
NYHA class 3 -4	30 (32.6%)	12 (22.2%)	18 (47.4%)	**.011**[a]
BMI	22.9 ± 1.5	23.1 ± 1.5	22.6 ± 1.5	.167
Diabetes mellitus, n (%)	5 (5.5%)	2 (3.7%)	3 (8.1%)	.365[b]
Hypertension, n (%)	17 (18.7%)	9 (16.7%)	8 (21.6%)	.551[b]
Hyperlipidemia, n (%)	13 (14.3%)	6 (11.1%)	7 (18.9%)	.296[b]
Family history, n (%)	11 (12.1%)	5 (9.3%)	6 (16.2%)	.317 [b]
Atrial fibrillation, n (%)	2 (2.3%)	1 (1.9%)	1 (2.8%)	.791[b]
ACEI/ARB, n (%)	73 (79.3%)	47 (82.5%)	26 (74.3%)	.347[b]
B-blockers, n (%)	77 (83.7%)	48 (84.2%)	29 (82.9%)	.865[b]
Digoxin, n (%)	22 (23.9%)	13 (22.8%)	9 (25.7%)	.751[b]
Echocardiography parameters				
Baseline				
LVEDD, mm	55.9 ± 5.1	54.3 ± 4.7	58.1 ± 4.8	<**.001**[a]
LVESD	43.7 ± 6.4	41.8 ± 5.6	46.4 ± 6.5	<**.001**[a]
LV Ejection fraction (%)	33.5 ± 6.3	35.2 ± 4.7	31.1 ± 7.5	**.002**[a]
Laboratory parameters				
Fasting glucose, mg/dl	92 (84–104)	92 (84–103)	94 (81–105)	.842[c]
NT-proBNP	582 (253–1377)	476 (225–1336)	755 (454–1421)	.249[c]
Urea, mg/dl	27 (20–35)	27 (20–36)	27 (22–35)	.766[c]
Creatinine, mg/dL	0.7 (0.6–0.8)	0.7 (0.6–0.9)	0.7 (0.6–0.8)	.324[c]
Uric acid, mg/dL	6.0 (4.8–7.8)	6.8 (4.8–8.0)	5.6 (4.8–6.6)	.429[c]
Protein, mg/dL	7.0 ± 0.7	7.1 ± 0.6	6.9 ± 0.7	.168[a]
Albumin, mg/dL	3.6 ± 0.4	3.8 ± 0.4	3.4 ± 0.3	<**.001**
Hemoglobin, g/dL	12.7 ± 1.6	12.9 ± 1.6	12.3 ± 1.6	.105[a]
WBC, cells/mL	8.0 (6.6–9.5)	8.0 (6.6–9.6)	8.0 (6.4–9.4)	.976[c]
Platelet count, cells/mL	286 ± 101	299 ± 77	268 ± 128	.191[c]
Lymphocyte, cells/mL	2.2 ± 0.8	2.5 ± 0.8	1.7 ± 0.4	<**.001**
Total cholesterol, mg/dL	170 (143–199)	171 (151–200)	156 (126–191)	.189[c]
Triglyceride, mg/dL	110 (85–162)	116 (93–162)	96 (83–171)	.369[c]
HDL cholesterol, mg/dL	44 ± 15	45 ± 13	43 ± 17	.428[a]
LDL cholesterol, mg/dL	90 (74–117)	98 (75–117)	88 (68–117)	.276[c]
TSH	1.9 (1.0–2.8)	2.1 (1.0–3.0)	1.4 (1.1–2.6)	.500[c]
PNI	47.5 ± 7.9	51.1 ± 7.1	42.5 ± 6.2	<**.001**[a]
PNI < 46.9	42 (45.7%)	21 (36.8%)	21 (60.0%)	**.003**[a]

Bold data displays statistically significant difference ($P < .05$).

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end sistolic diameter, NT-proBNP = N terminal pro brain natriuretic peptide, NYHA = New York Heart Association, PNI = prognostic nutritional index, WBC = white blood cell count.

[a] Students *t* test.

[b] Pearson chi-square.

[c] Mann–Whitney *U* test.

18.7% had a history of hypertension; a total of 12.1% had a family history of dilated cardiomyopathy, around 5.5% were diabetic, a total of 14.3% were dyslipidemic, and 2.3% had a history of atrial fibrillation (AF). The majority of women were treated with optimal therapy for HF (beta blockers and ACEI/angiotensin receptor blockers [ARBs]). No significant differences in medical therapy after diagnosis between the two groups were observed with respect to use of beta blockers and ACEI/ARBs as shown in Table 1.

3.2. Clinical outcomes

During a follow-up period of median 67.0 (12.0–192.0) months, 44.6% of patients had LV recovery with improvement in cardiac symptoms during the follow-up period, whereas 55.4% of patients had persistent LV systolic dysfunction during their last follow-up. No significant difference between the two groups in terms of age and co-morbidities such as hypertension, dyslipidemia, diabetes mellitus, AF, and family history of dilated cardiomyopathy were noted. LVEDD were significantly increased, and LVEF was significantly lower in patients with adverse cardiac event. Also serum albumin concentration and lymphocyte count, which are components of PNI calculation, were significantly lower in patients with adverse cardiac event. Other laboratory parameters were similar between the groups. The mean PNI of patients with adverse cardiac event or not were 42.5 ± 6.2 and 51.1 ± 7.1, respectively. Table 2 presents primary and secondary clinical outcomes of the study according to PNI values. During follow-up period, primary composite endpoint developed in 35 of 92 subjects (38.0%). Cardiovascular death was significantly higher in the group with lower PNI (14.3% vs 0%; $P = 0.006$). Patients in the lower PNI group had a higher incidence of hospitalization due to worsening HF (35.7% vs 28.0%; $P = .083$). Persistent LV systolic dysfunction also

Table 2

Comparison of study endpoints according to the PNI values.

Parameter	All *n*=92	Low PNI (< 46.9) *n*=42	High PNI (>46.9) *n*=50	*P*
Primary composite endpoint	35 (38.0%)	21 (50.0%)	14 (28.0%)	**.003**
Secondary endpoints				
Cardiovascular death	6 (6.5%)	6 (14.3%)	0 (0.0%)	**.006**
Hospitalization for worsening HF	29 (31.5%)	15 (35.7%)	14 (28.0%)	.083
LV non-recovery	51 (55.4%)	33 (78.6%)	18 (36.0%)	**.001**

HF = heart failure, PNI = prognostic nutritional index.
Bold data displays statistically significant difference ($P < .05$)

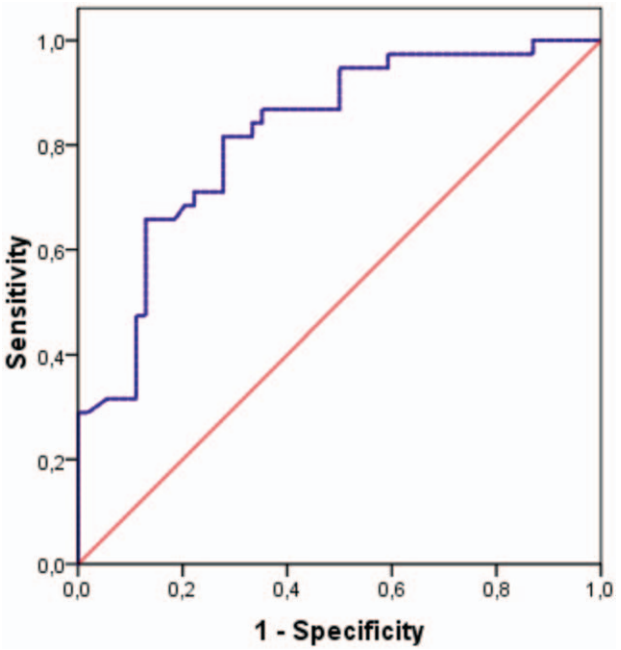

Figure 1. Receiver-operating characteristic curve of the PNI for predicting primary endpoint. PNI = prognostic nutritional index.

developed more frequently in the lower PNI group (78.6% vs 36%; $P = .001$).

According to the ROC curve analysis, the best cut-off value of PNI to predict adverse cardiac events was 46.9 (Fig. 1). A Kaplan–Meier analysis showed a significantly lower primary composite endpoint-free survival rate in patients with low PNI (log-rank, $P = .018$) (Figure 2).

Univariate cox regression analyses showed that initial LVEF, LVEDD, LVESD, the presence of NYHA class 3-4 and PNI, serum albumin concentration and lymphocyte counts, were significantly associated with the primary endpoint as shown in Table 3. PNI and the presence of NYHA 3-4 were independent predictors of the primary endpoint when PNI analyzed as a continuous variable (Model 1, odds ratio 0.805; 95% confidence interval 0.729–0.888; $P < .001$ and odds ratio 4.473; 95% confidence interval 1.279–15.636; $P = .019$). Using a cutoff level of PNI < 46.9 was an independent predictor of the primary endpoint (Model 2, odds ratio 6.590; 95% confidence interval 2.275–19.089; $P = .001$) (Table 4).

4. Discussion

In the present study, it was examined whether nutritional status assessed by PNI was associated with adverse outcomes in patients with PPCMP. Patients in the low PNI group had higher risk for cardiovascular death or hospitalization due to worsening HF as

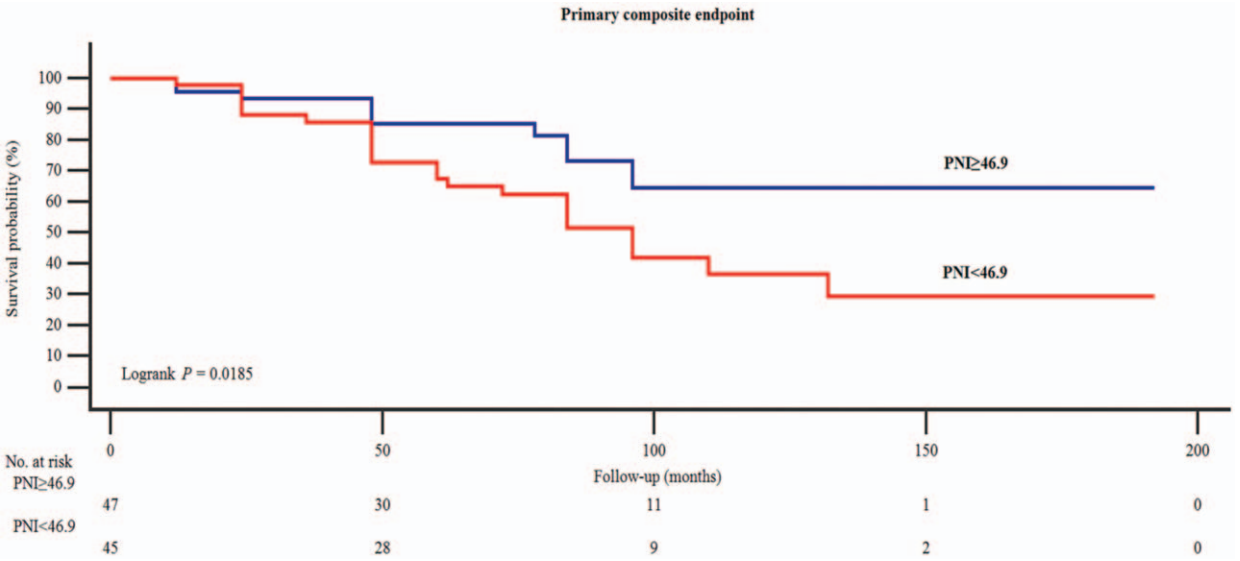

Figure 2. Kaplan–Meier curve analysis of the composite primary endpoint.

Table 3

Univariate cox proportional hazard models for prediction of primary endpoint.

	Univariate analysis		
Variable	**HR**	**95% CI**	***P*-value**
Age at diagnosis	0.940	0.874–1.010	.092
NYHA class 3-4	0.415	0.194–0.889	.024
BMI	1.027	0.827–1.274	.811
Diabetes mellitus	1.025	0.138–7.595	.981
Hypertension	1.503	0.571–3.955	.409
Hyperlipidemia	0.953	0.359–2.528	.923
Family history	0.730	0.252–2.117	.562
Atrial fibrillation	1.257	0.988–20.355	.704
ACEI/ARB	1.877	0.793–4.441	.152
B-blockers	0.563	0.076–4.169	.574
Digoxin	0.582	0.268–1.264	.171
LVEDD	1.084	1.005–1.170	.037
LVESD	1.063	1.006–1.123	.030
LVEF	0.934	0.877–0.995	.033
Fasting glucose	1.001	0.995–1.007	.751
NT-proBNP	1.000	1.000–1.000	.506
Urea	0.990	0.968–1.014	.408
Creatinine	0.199	0.029–1.357	.099
Uric aside	1.021	0.863–1.207	.811
Protein	0.687	0.416–1.134	.142
Albumin	0.406	0.206–0.800	<.009
Hemoglobin	0.799	0.631–1.012	.063
WBC	1.058	0.961–1.166	.251
Platelet	1.002	0.998–1.006	.264
Lymphocyte	0.473	0.278–0.805	<.006
Total cholesterol	1.001	0.998–1.003	.498
Trigliseride	1.001	0.999–1.003	.284
HDL cholesterol	0.988	0.966–1.011	.296
LDL cholesterol	0.998	0.985–1.011	.737
TSH	1.035	0.828–1.294	.761
PNI	0.930	0.883–0.979	<.005
PNI < 46.9	0.250	0.087–0.721	<.010

Bold data displays statistically significant difference ($P < .05$).

CI = confidenceinterval; HDL-C = high-density lipoprotein cholesterol, HR = hazardratio; LDL-C = low-density lipoprotein cholesterol, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end sistolic diameter, NT-proBNP = N terminal pro brain natriuretic peptide, NYHA = New York Heart Association, PNI = prognostic nutritional index, WBC = white blood cell count.

Table 4

Multivariate cox proportional hazard models for prediction of primary endpoint.

Variables	**HR**	**95%CI**	***P*-value**
Model 1			
NYHA class 3-4	0.281	0.107–0.739	**.010**
LVEDD	0.946	0.837–1.068	.369
LVESD	1.061	0.974–1.156	.173
LVEF	0.948	0.883–1.018	.140
PNI	0.895	0.839–0.955	**.001**
Model 2			
NYHA class 3-4	0.419	0.177–0.989	**.047**
LVEDD	0.975	0.873–1.088	.645
LVESD	1.055	0.969–1.148	.215
LVEF	0.952	0.886–1.022	.171
PNI < 46.9	0.200	0.067–0.599	**.004**

Bold data displays statistically significant difference ($P < .05$).

LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end sistolic diameter, NYHA = New York Heart Association, PNI = prognostic nutritional index.

well as persistent LV systolic dysfunction. Furthermore, when analyzed as a continuous variable, low PNI value predicted increased risk for adverse events in patients with PPCMP. The ROC analysis indicated that PNI predicted adverse events using a cut-off level of 46.9. To the best of our knowledge, the present study is the first to identify the long-term prognostic value of PNI in PPCMP patients.

PPCM is an idiopathic cardiomyopathy with a significant probability of myocardial recovery. The exact pathophysiologic mechanism that leads to PPCM remains unknown, but multiple possible etiologies including viral myocarditis, nutritional deficiencies, autoimmunity, increased oxidative stress and inflammation, vascular dysfunction, hormonal insults, and underlying genetics have been suggested in the pathogenesis of cardiomyopathy.[6] Previous studies have showed that many women with PPCM recover their LV function partially or fully; however, persistent LV systolic dysfunction can be associated with adverse cardiac events including lethal ventricular tachyarrhythmias, thromboembolic complications, and even death.[18–20] The recovery rate from PPCM appears to be widely heterogeneous. Unfortunately, there are no specific and exact predictors of whether or not myocardial recovery will occur. Various factors that predict outcomes in patients with PPCM have previously been proposed but not validated. These factors include decreased LVEF and degree of LV dilatation at diagnosis, presence of LV thrombus, lower systolic blood pressure and higher resting heart rate.[21] Several studies have demonstrated a correlation between lower LVEF and increased LV diameters at the time of diagnosis, which results in worse outcome in these women. As previously reported, our results were similar and lower baseline LVEF and higher LVEDD from echocardiographic findings were found as significant predictors of persistent LV dysfunction and adverse events. Some other studies indicated that NYHA functional class, N-terminal prohormone of brain natriuretic peptide, and increased plasma markers of inflammation and apoptosis at diagnosis are predictors of poor outcome as well.[22–25]

Blauwet et al have reported that lower BMI and total cholesterol at baseline were both associated with poor outcome in patients with PPCM.[26,27] Other similar studies have shown that increased BMI is associated with decreased all-cause mortality in patients with chronic HF.[22,28,29] Several hypotheses have been suggested to explain these results, including the idea that overweight and obese patients may have higher metabolic reserve, reduced cytokine and neuroendocrine activation and higher blood pressure that may allow more aggressive upwards titration of medications. Cardiac cachexia is a serious presentation of the catabolic status in advanced HF, which occurs when resting metabolic rate increases and gastrointestinal malabsorption prevails in patients with advanced disease. The pathophysiology may involve diminished perfusion to the gut and disturbed microcirculation of the intestine, resulting in local edema, abnormal mucosal permeability for endotoxin and subsequent inflammation.[12,30]

Serum albumin level and BMI are often used as indicators of nutritional status in routine clinical practice.[31] However, serum albumin level is influenced by several non-nutritional factors including fluid status, hepatic congestion, renal dysfunction (albuminemia) and inflammation in patients with HF. Similarly, BMI is influenced by fluid status, indicating that the measurement of albumin or BMI alone is an insufficient approach in measuring nutritional risk.

PNI, which is calculated based on the serum albumin concentration and total lymphocyte count in the peripheral blood, may theoretically represent both malabsorption and chronic inflammation in HF.[31] Our study suggests that PNI is a useful index to predict adverse outcomes in patients with PPCM. To our knowledge, there is no study in the literature on the association between PPCM and PNI in predicting adverse outcomes and our study is the first in the literature that investigates the possible relation between PNI and PPCM up to the present.

PNI was first reported by Buzby et al as an objective nutritional risk index in 1980 and then Onodera et al have reported the association between PNI and surgical risk for patients with malignancy.[32,33] PNI has been used as a predictive nutritional marker in patients with various diseases, such as malignancy, acute or chronic HF and STEM.[16,17,34] Malnutrition is a complex state that involves protein reserve reduction, caloric collapse and immune defense weakening. Nakagomi et al have shown that malnutrition was significantly associated with higher concentrations of inflammatory markers in patients with chronic HF.[35] Several other nutritional screening tools such as Subjective Global Assessment, Mini Nutritional Assessment Screening Form, Malnutrition Universal Screening Tool and Nutritional Risk Screening 2002 are available for nutritional risk assessment in patients.[36] These indices require subjective assessment, which may be affected by the examiner's experience. In addition, they require body weight change, which is affected by fluid status in hospitalized patients with HF. In contrast, PNI consists of simple objective measurements, which can be easily obtained upon admission in patients with HF. Therefore, PNI may be more applicable in HF patients than other indices but there are not enough studies on this subject in the literature. Further investigations are necessary to evaluate which nutritional index is more specific to patients with HF.

There are several potential explanations for the relationship between low PNI and cardiovascular or non-cardiovascular mortality in patients with PPCMP. Low PNI is accompanied by hypoalbuminemia, reflecting malnutrition and inflammation, which are associated with worse HF outcome. Serum albumin is well-recognized as an important biomarker for long-term malnutrition and systemic stress response. Hypoalbuminemia, a well-regarded component for risk indication, is easily measured through routine laboratory and is associated with increased mortality in several non-cardiac co-morbidities such as end-stage renal disease, infection, and pulmonary disease. However, serum albumin levels are influenced by numerous factors including fluid shift, hepatic failure and infection, in addition to metabolic stress and catabolic states.[31] Several other serum proteins such as transferrin and prealbumin are considered as parameters for evaluation of malnutrition. Since blood levels decrease earlier than albumin, they are very sensitive parameters in early malnutrition detection. However, prealbumin concentration in plasma, like that of albumin, is affected by changes in transcapillary escape. Hence, interpretation of plasma prealbumin is difficult in patients with infections, inflammation, or recent trauma. PNI permits quantification of the interaction between HF, inflammation and malnutrition using both albumin level and total lymphocyte count, which is a second indicator for inflammation. The physiological stress induced by advanced heart failure results in an increased production of cortisol and a shift in the leukocyte differential toward a decreased percentage of lymphocytes (%L).[37] Lymphocyte concentration is a readily available, inexpensive, and simple prognostic marker in patients with symptomatic heart failure who do not have corticosteroid use, recent trauma, myocardial infarction, infection, surgery, or history of malignancy. Lymphopenia has been described in numerous advanced disease states, including HF. In the lights of these findings PNI appears to generate a potent indicator for diverse mechanisms of malnutrition, including neurohormonal disorders, decreased caloric intake and impaired perfusion, in patients with HF by combining albumin and lymphocyte levels. This may explain the increased cardiovascular and non-cardiovascular mortality of patients in the low PNI group.

Nutritional status evaluation is recommended in the guidelines in patients with HF and some studies have reported that nutritional intervention may be beneficial for these patients. However, no study has investigated patients with PPCMP. It remains uncertain how patients with low PNI should be managed. Further investigations are required to evaluate whether nutritional interventions improve clinical outcomes in PPCMP patients.

5. Limitations

Our study has several limitations. First; this was a single center, retrospective, observational study. Second; PNI levels were evaluated only once and did not assess their changes over time during the follow-up period. Third; because of methodological limitations of retrospective analysis, it is not possible to define the exact causal relationship between PNI level and adverse cardiovascular outcomes. In addition, more sensitive protein levels such as prealbumin could not be evaluated due to the retrospective design of our study. Although a relatively large series of patients with PPCM were assessed, the study population was small in size due to the rarity of PPCM. Hence, the small sample size may limit the power of statistical test in revealing significant predictors and demonstrating the effects of PNI on different subgroups. Further prospective investigations on larger cohorts are necessary to confirm our findings, to clarify the underlying mechanism and to elucidate the prognostic utility of PNI more accurately.

6. Conclusion and future perspectives

This study identified nutritional status assessed by the PNI, a simple index calculated from routine biochemistry and hemogram tests, as an independent predictor of long-term cardiovascular outcomes in PPCMP patients. Lower PNI scores were associated with adverse cardiovascular outcomes. This result confirmed that nutritional and immunological situations are important when considering the long-term outcome in patients with PPCMP. Our study suggested that the PNI might be useful for risk stratification of PPCMP patients in clinical practice. Further investigations on independent multicenter cohorts should be performed in order to validate our findings.

Author contributions

Conceptualization: Bahar Tekin Tak, Serkan Cay, Firdevs Aysenur Ekizler.
Supervision: Serkan Cay.
Validation: Ozcan Ozeke, Firat Ozcan, Serkan Topaloglu, Dursun Aras.
Visualization: Bahar Tekin Tak, Serkan Cay, Habibe Kafes, Elif Hande Ozcan Cetin.

Writing – review & editing: Bahar Tekin Tak, Serkan Cay, Habibe Kafes, Elif Hande Ozcan Cetin, Nedret Ulvan

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