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Original Article

Low prognostic nutritional index is associated with adverse outcomes in patients with hypertrophic cardiomyopathy

Düşük prognostik nütrisyonel indeks hipertrofik kardiyomiyopatili hastalarda kötü sonuçlar ile ilişkilidir

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Abstract

Aim: The aim of the study was to investigate poor nutritional status assessed by prognostic nutritional index (PNI) on the prognosis of patients with hypertrophic cardiomyopathy(HCM).

Material and Methods: A total of 420 patients with HCM were assessed. The primary end point was defined as the occurrence of CV death that included sudden cardiac death (SCD), death due to HF and cardioembolic stroke-related death.

Results: During the follow-up, primary end point was developed in 25 (6.0%) patients. Receiver operating characteristic (ROC) analysis showed that using a cut-off level of 40, PNI predicted the occurrence of primary end point with a sensitivity of 76% and specificity of 76.7%. In the multivariate model, low PNI was significant predictor of the primary end point.

Conclusion: This study showed that lowerPNI level is an independent predictor of CV death in patients with HCM.

Keywords: cardiovascular death; hypertrophic cardiomyopathy; prognostic nutritional index

Öz

Amaç: Çalışmanın amacı prognostik beslenme indeksi (PNI) ile değerlendirilen zayıf beslenme durumunun, hipertrofik kardiyomiyopatili (HKMP) hastaların prognozu üzerine etkisini araştırmaktır.

Gereç ve Yöntemler: Toplam 420 HKMP hastası değerlendirildi. Çalışmanın birincil sonlanım noktası, ani kardiyak ölüm (AKÖ), kalp yetmezliği (KY) nedenli ölüm ve kardiyo embolik inme ilişkili ölümü içeren kardiyovasküler ölüm saptanması olarak tanımlandı.

Bulgular: Takip süresi boyunca 25 (% 6.0) hastada birincil sonlanım noktası saptandı. ROC (Receiver operating characteristic curve) analizi, PNİ kesme seviyesi 40 kullanarak PNİ'nin % 76 hassasiyet ve% 76.7 özgüllük ile birincil son nokta oluşumunu öngördüğünü gösterdi. Tek değişkenli ve çok değişkenli modelde düşük PNİ değeri, primer sonlanım noktası için önemli bir belirleyici olarak saptandı.

Sonuç: Bu çalışma, düşük PNİ düzeyinin HKMP hastalarında KV ölümün bağımsız bir öngördürücüsü olduğunu göstermiştir.

Anahtar kelimeler: kardiyovasküler ölüm; hipertrofik kardiyomiyopati; prognostik nütrisyonel indeks

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Volume 11 Number 3 p: 136-145

Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic cardiomyopathies characterized by ventricular hypertrophy, myocardial fibrosis, and impaired ventricular relaxation[1]. Myocyte hypertrophy and disarray, interstitial fibrosis as well as small vessel disease are main pathological trademarks of the myocardium in HCM[2]. The clinical course of HCM is highly variable, ranging from asymptomatic status with a normal life expectancy to adverse clinical outcomes such as severely limiting dyspnea, advanced heart failure (HF), systemic embolic events, stroke, malignant arrhythmic events and sudden cardiac death. The annual mortality rate of HCM patients is thought to be about 1%. Sudden cardiac death (SCD) and embolic stroke are major causes of death in patients with HCM[3, 4]. In addition, some patients develop systolic dysfunction causing increased morbidity and mortality[5]. Identifying high-risk HCM patients plays a key role in risk stratification, treatment strategy selection, preventing complications and improving outcomes. Although a set of clinical risk factors and imaging results are investigated for risk stratification in HCM patients presently, the clinical outcomes of HCM are still broadly unpredictable given that HCM is generated by various etiologies, has a genetic diversity with heterogeneous and complex clinical expression and the pathophysiological mechanisms are very complicated.

In recent decades, much attention has been given to assess the role of inflammation and oxidative stress in both for pathogenesis and to determine the prognosis of HCM. Several studies established increased circulating inflammatory markers in HCM such as TNF-α, IL-6, MCP-1 and monocyte count to high-density lipoprotein cholesterol ratio(MHR), neutrophil-to-lymphocyte ratio (NLR)[6-9]. Recent studies have shown that poor nutritional status is associated with increased inflammation and neurohormonal activation, indicating poor prognosis in various cardiovascular diseases. 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[10, 11]. Although nutritional status examination is more complex, objective and well-recognised 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 immuno-nutritional status of patients[12]. 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). However this association has not been previously assessed in patients with HCM. The aim of the present study was to evaluate PNI on the clinical end points in patients with HCM.

Material And Methods

Study population

The study population included 442 consecutive patients clinically diagnosed with HCM at our hospital between October 2003 and December 2016. A diagnosis of HCM was made based on the current guidelines of the American College of Cardiology / European Society of Cardiology (ACC/ ESC), was the presence of a hypertrophied left ventricle with a maximal wall thickness of ≥15 mm on echocardiography in patients without alternative explanations capable of producing a similar degree of hypertrophy or systemic diseases. Individuals with metabolic diseases (e.g, Anderson Fabry disease) and related syndromes (e.g, Noonan syndrome) were eliminated. Patients with clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers such as active cancer, active infection, renal or hepatic insufficiency, chronic inflammatory disease, congenital heart disease, cardiac valve disease were excluded from study. Also patients without a recorded measurement of admission laboratory parameters and sufficient clinical information were excluded. According to these exclusion criteria, 22 patients were excluded from the study and a total of 420 patients were included in the study. Data regarding clinical features, risk profiles, laboratory and echocardiographic parameters of all patients were collected from clinical follow-up visits, patients' files and the electronic database The present study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Echocardiography

On admission to the hospital, all patients underwent transthoracic echocardiography using commercially available ultrasound equipment. They had undergone two-dimensional and M-mode echocardiography with continuous, pulsed and colour Doppler imaging at the time of diagnosis and the last follow-up visit with the Vivid 7 system (GE Healthcare, Wauwatosa, Wisconsin). EF was calculated by using modified Simpson method. Maximum wall thickness was accepted as the greatest thickness in any single segment and was evaluated at end-diastole on the basal, mid or apical short-axis views. LV outflow tract obstruction was measured either in a

rest state or during a Valsalva maneuver. Obstructive HCM was defined as LV outflow tract obstruction >30 mmHg.

Laboratory parameters

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. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in metres. Patients were considered to have hypertension if their blood pressure was ≥140/90 mmHg 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. PNI was calculated using the following formula: 10 x serum albumin value (g/dL) + 0.005 x total lymphocyte count in the peripheral blood (per mm^3). Patients were divided into two groups according to their admission PNI.

Definitions & study end points

The primary end point was defined as the occurrence of CV death that included sudden cardiac death (SCD), death due to HF and cardioembolic stroke-related death. SCD was accepted unexpected and instantaneous collapse leading to death due to any cardiac cause occurring in the absence of symptoms or within 1 h of the onset of symptoms in a patient who had previously experienced a relatively stable or uneventful clinical course or witnessed unexpected death. HF related death was accepted as death preceded by symptoms of heart failure >1h. [13]. The follow-up duration was commenced with the first visit and ended with the occurrence of death or the last visit. Follow up for clinical end points was performed by review of medical records in our hospital. We decided a cardiac event that occurred outside our hospital by phone calls with patients, their relatives and/or their general practitioners. The cause of death was assessed by evaluating the hospital records, official hospital release forms or death certificates obtained from National Survival Registry. All-cause death and presence of NYHA III-IV symptoms were defined as secondary end points.

Statistical analysis

Statistical analysis was performed using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Inc., IL, and USA). Continuous variables were presented as mean ± 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 Student's t test for normally distributed variables and Mann–Whitney U test for variables without normal distribution. The Chi-square or Fisher's exact test was used to compare categorical variables as appropriate. The association between PNI and development of adverse outcomes of HCM were estimated with univariate and multivariate Cox proportional hazards regression analyses. Survival estimates were calculated by the Kaplan-Meier method and the long-rank test was used for comparison. Receiver operating characteristic curve (ROC) analysis was used to determine the optimum cut-off levels of PNI to predict primary end point. A p-value < 0.05 (using a two-sided test) was considered significant.

Results

We assessed consecutive 420 patients with HCM in this study. Baseline clinical, demographic echocardiographic and laboratory characteristics of the study population were summarized in Table 1. A total of 244 patients (58.1%) were male, and the mean age of the study population was 48.4 ±15.2 years old. After a median (interquartile range) follow-up period of 6.0 (5.0–8.0) years, primary end point was developed in 25 (6%) subjects (sudden death in 10 (2.4 %), death for progressive HF in 14 (3.3 %) and cardioembolic stroke-related death in 1 (0.2 %)). Patients with CV death had a higher prevalence of atrial fibrillation (44.0% vs.18.2%, p =0.002), higher NYHA class (68.0% vs. 12.7%, p <0.001), higher left atrial diameter (LA) (43.8 ± 4.4 mm vs. 40.9 ± 5.4 mm, p = 0.013), lower ejection fraction (EF) (53.6 ±10.5 mm vs. 60.8 ±7.4 mm, p < 0.001) and higher level of C-reactive protein (CRP) (11.3 (4.8-22.7) vs. 4.8 (3.9-5.8), p< 0.001) compared the patients without CV death. Also serum albumin concentration, serum lymphocyte count and PNI values (37.5±5.0 vs. 43.7 ±4.8, p < 0.001) were significantly lower in patients with CVD than in patients without CV death. Follow-up data and clinical outcomes regarding primary and secondary end points were presented in Table 2. During follow-up period, all-cause death was observed in 34 subjects (8.1%) and presence of NYHA III-IV symptoms was observed in 66 subjects (15.7 %) which were the secondary end points among the study population. Low PNI values were significantly associated with both primary and secondary end points of the study.

We also compared baseline clinical characteristics of the study patients according to PNI levels (Table 3). The patients in low PNI group (<; n = 140) had a higher prevalence of atrial fibrillation, higher NYHA class, larger LA dimension, larger left ventricular enddiastolic diameter (LVEDD), lower EF, higher values of CRP and lower values of lymphocyte and albümin counts than the patients in high PNI group.

Volume 11 Number 3 p: 136-145

Table 1. Baseline clinical, echocardiographic and laboratory characteristics of the study patients according to the presence of cardiovascular death

Variables	Total n = 420	CV Death(+) n = 25	CV Death (–) n = 395	p value
Age	48.4 ±15.2	49.6± 14.8	48.4± 15.2	.692
Gender (Male), n (%)	244 (58.1%)	13 (52.0%)	231(58.5%)	.524
Hypertension n (%)	74 (17.6%)	5 (20.0%)	69 (17.5)	.747
Diabetes n (%)	66 (15.7%)	5 (20.0 %)	61 (15.4%)	.544
Smoking n (%)	63 (15.0%)	4 (16.0%)	59 (14.9%)	.885
Body-mass index (kg/m2)	26(24-29)	25(23-27)	26 (24-29)	.108
Coronary artery disease	131 (31.2%)	7(28.0%)	124 (31.4 %)	.723
Atrial fibrillation	83 (19.8%)	11 (44.0 %)	72 (18.2%)	.002
NYHA III or IV, n (%)	67 (16.0%)	17 (68.0%)	50 (12.7%)	<.001
β-blocker, n (%)	397 (94.5 %)	23 (92.0%)	374(94.7%)	.567
Amiodarone,n (%)	10 (2.4%)	1 (4.0%)	9 (2.3%)	.584
Echocardiographic parameters				
LVEDD (mm)	42 (40-46)	43 (40-47)	42 (40-46)	.800
Maximal LV wall thickness (mm)	20.7 ± 4.7	20.7± 4.6	20.7± 4.7	.990
LVEF (%)	60.4±7.8	53.6 ±10.5	60.8 ±7.4	<.001
LVOT Gradient (mmHg)	24.1 ±33.1	12.6 ±23.5	24.8 ±33.5	.072
LA diameter (mm)	41.1 ± 5.4	43.8± 4.4	40.9± 5.4	.013
SPAB	30 (28-35)	35 (30-40)	30 (28-35)	.003
Apical aneurysm, n (%)	16 (3.8 %)	1 (4 %)	15 (3.8 %)	.959
Syncope	57 (13.6%)	1(4.0%)	56 (14.2 %)	.150
Family history	76 (18.1%)	5(20.0%)	71 (18.0%)	.799
NSVTat 24 Hour Holter monitoring	70 (16.7%)	7 (28.0%)	63 (15.9%)	.117
Laboratory parameters				
Hemoglobin (g/dl)	13.4 ±3.1	13.0 ±1.6	13.5 ±3.1	.454
WBC (×103 µL)	8.2±5.2	8.0±2.9	8.3 ±5.3	.843
Neutrophil (×103 µL)	5.0±2.0	5.3±2.7	4.9 ±1.9	.381
Lymphocyte (×103 µL)	2.3±0.6	1.8±0.4	2.3±0.6	<.001
Monocyte (×103 µL)	591 ±254	680±284	585 ±252	.072
Platelet (×103 µL)	235 (198-293)	218(182-300)	236(198-291)	.485
Glucose, mg/dL	112±45	115 ±53	112±45	.782
Creatinine (mg/dl)	0.9 (0.8-1.0)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	.855
Uric acid (mg/dl)	6.0 (5.3-6.5)	6.3 (5.1-7.5)	5.9 (5.4-6.5)	.174
TSH, UI/mL	1.6 (1.0-2.3)	1.6 (0.9-2.6)	1.6 (1.1-2.3)	.802
Albumin (g/dl)	4.3± 0.5	3.7± 0.5	4.3± 0.4	<.001
PNI	43.3± 5.0	37.5 ±5.0	43.7±4.8	<.001
hsCRP	4.8 (4.0-5.8)	11.3 (4.8-22.7)	4.8 (3.9-5.8)	<.001

Data are presented mean ± SD or n (%).
CRP: C-reactive protein; LA: Left atrium; LVEDD: left ventricular enddiastolic diameter; LVEF: left ventricular ejection fraction; ; LVOT: left ventricular outflow tract; NSVT: non sustained ventricular tachycardia; NYHA: New York Heart Association; PNI: prognostic nutritional index; TSH: thyroid-stimulating hormone; WBC: white blood cell

Table 2. Comparison of primary and secondary endpoints according to the PNI values

Parameter	All n=420	Low PNI n = 140	High PNI n = 280	P
Cardiovascular death	25(6.0 %)	19 (13.6 %)	6(2.1%)	<.001
Sudden cardiac death	10 (2.4 %)	7 (5 %)	1 (0.4 %)	0.013
Heart failure related death	14 (3.3 %)	12 (8.6 %)	2 (0.7 %)	<.001
Stroke related death	1 (0.2 %)	0 (0.0 %)	1 (0.4 %)	.480
All-cause death	34 (8.1 %)	27 (19.3 %)	7 (2.5 %)	<.001
NYHA III or IV	66 (15.7 %)	52 (37.1 %)	14 (5.0 %)	<.001

Table3. Comparison of the baseline characteristics among the quantiles of PNI

Variables	Low PNI(+) n = 140	High PNI (–) n = 280	p value
Age	50.4± 15.5	47.5± 14.9	.407
Gender, Male n (%)	83 (59.3%)	161 (57.5%)	.727
Hypertension n (%)	29 (20.7%)	45 (16.1)	.239
Diabetes n (%)	25 (17.9%)	41 (14.6%)	.394
Smoking n (%)	26 (18.6%)	37 (13.2%)	.147
Body-mass index (kg/m2)	26(24-28)	27(24-29)	.103
Coronary artery disease	48 (34.3%)	83 (29.6 %)	.333
Atrial fibrillation	36 (25.7 %)	47 (16.8%)	.030
NYHA III or IV n (%)	57 (40.7%)	10 (3.6%)	<.001
Echocardiographic parameters			
LVEDD (mm)	45 (41-48)	42 (39 -45)	<.001
Maximal LV wall thickness (mm)	20.3± 3.7	20.9 ± 5.1	.199
LVEF (%)	56.8 ±9.4	62.1 ±6.2	<.001
LVOT Gradient (mmHg)	20.0 ±33.6	26.1 ±32.7	.075
LA diameter (mm)	42.8± 5.3	40.3± 5.3	<.001
SPAB	33 (30-40)	30 (28-35)	<.001
Syncope	17(12.1%)	40 (14.3 %)	.546
Family history	18 (12.9%)	58 (20.7%)	.059
NSVTat 24 Hour Holter monitoring	29 (20.7%)	41 (14.6%)	.116
Laboratory parameters			
Hemoglobin (g/dl)	13.0 ±2.3	13.6 ±3.3	.077
WBC (×103 µL)	8.2±2.6	8.3 ±6.0	.933
Neutrophil (×103 µL)	5.2 ±2.3	4.8 ±1.8	.082
Lymphocyte (×103 µL)	2.1±0.7	2.4±0.5	.<.001
Monocyte (×103 µL)	600 ± 249	586 ±257	.604
Platelet (×103 µL)	227 (189 -275)	240 (201 -304)	.041
Glucose, mg/dL	121 ± 56	108 ± 38	.011
Creatinine (mg/dl)	0.9 (0.8-1.1)	0.8 (0.7-1.0)	.041
Uric acid (mg/dl)	5.9 (5.1-6.7)	6.0 (5.4-6.5)	.723
TSH, UI/mL	1.4 (1.0-2.3)	1.6 (1.1-2.3)	.619
Albumin (g/dl)	3.7± 0.2	4.6± 0.3	<.001
hsCRP	4.9 (4.3-8.8)	4.7 (3.4-5.7)	.009

Data are presented mean ± SD or n (%).
CRP: C-reactive protein; LA: Left atrium; LVEDD: left ventricular enddiastolic diameter; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NSVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; PNI: prognostic nutritional index; TSH: thyroid-stimulating hormone; WBC: white blood cell

Area under the curve was 0.817 (95% CI: 0.777–0.853; p <0.001). Using a cut-off level of 40.0, PNI predicted the occurrence of primary end point with a sensitivity of 76% and specificity of 76.7% (Figure1). A Kaplan–Meier analysis showed a significantly lower primary endpoint-free survival rate in patients with low PNI (log rank, P <0.0001, Figure 2). Also, patients with low PNI had a higher all cause death and NYHA III-IV symptoms compared with patients with high PNI (Figure 3). Univariate Cox regression analyses showed that atrial fibrillation, NYHA III-IV, LVEF, LA diameter, CRP and low PNI were significantly associated with the primary end point (for all; p < 0.05) (Table 4). However, in the multivariate model, low PNI (HR: 4.8; 95% CI: 1.6-14.4; p=0.005) and CRP (HR: 1.04; 95% CI: 1.006-1.074; p=0.019) were significant predictors of the primary end point (Table 4).

Volume 11 Number 3 p: 136-145

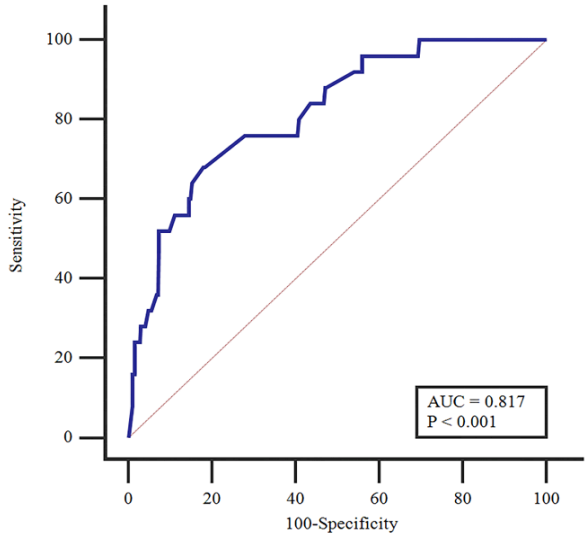

Figure 1: Receiver operating characteristic curve analysis of PNI to predict cardiovasculer death (primary end point) in patients with hypertrophic cardiomyopathy.

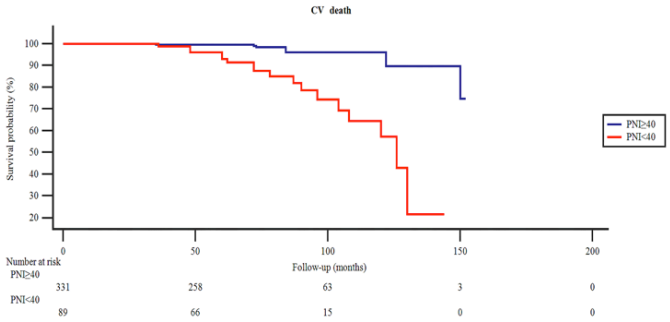

Figure 2: Kaplan–Meier analysis for primary end point according to PNI cut-off 40.0 in patients with hypertrophic cardiomyopathy.

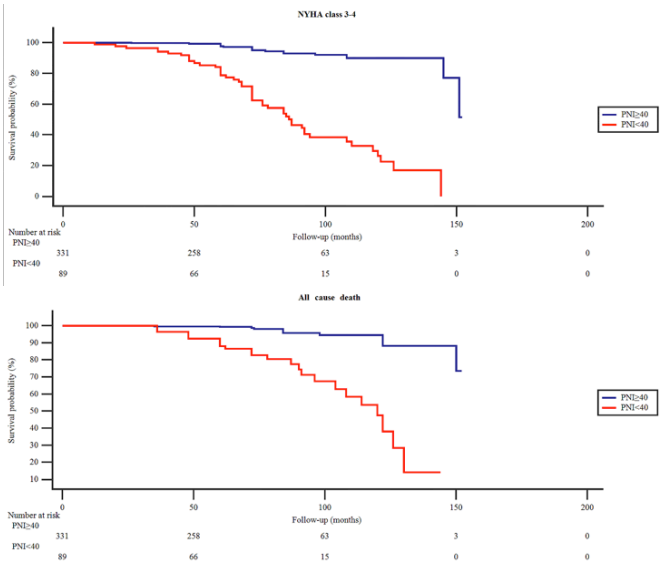

Figure 3: Kaplan–Meier analysis for secondary end points according to PNI cut-off 40 in patients with hypertrophic cardiomyopathy.

Discussion

This study showed that low PNI was associated with adverse outcomes in patients with HCM. The study's most important findings are the following: (1) Cardiovascular death significantly higher in the low PNI group; (2) all cause death significantly higher in the low PNI group; low PNI was significantly associated patients with presence of NYHA III or IV symptoms.

HCM is a common genetic cardiac disease characterized by LV hypertrophy, myofibrillar disarray and myocardial fibrosis. The clinical course of the disease is highly heterogeneous: many patients have no or moderate symptoms throughout their lifetime, but in some patients, HCM may lead to severe symptoms such as heart failure or even may result sudden cardiac death. Although the risks of sudden cardiac death have mostly dominated the HCM literature, progressive inability and heart failure is also a crucial complication of the disease. Heart failure is usually associated with left atrial enlargement, which reflects increased left ventricular filling pressures secondary to predominantly caused by diastolic dysfunction. In addition to diastolic dysfunction, some patients with severe LVH experience LV wall thinning and develop progressive left ventricular systolic dysfunction during their clinical course. Although previous studies have reported the progression of wall thinning detected in up to 15% of patients with HCM, Thaman et al demonstrated that wall thinning ≥5 mm occurred in 58% of patients with severe LVH. Impairment of the systolic function in hypertrophic cardiomyopathy below cut-off point set at 50% was previously shown to have crucial impact on the poor prognosis of patients with regard to major adverse event rates.

Reported HCM-associated mortality risk has undergone considerable modification over time. Recently, mortality in adult patients has reduced to approximately 0.5% per year owing to treatment interventions, especially implantable cardioverter defibrillators (ICD) and heart transplantation. Moreover, because the sudden death rate in HCM patients has reduced as a result of growing usage of ICDs, death due to heart failure is coming up as the prevalent mode of demise. In our study, presence of NYHA III-IV symptoms were seen in 66 (15.7%) patients and death due to HF in 14 (3.3%) patients. Pasqualucci et al showed that in a significant percentage of HCM patients, mortality can occur within 3 years after HF symptoms onset, in spite of a preserved LVEF [14]. Maron et al evaluated the nonobstructive HCM patients and

Table 4. Univariable and multivariable cox regression analysis for prediction of CVD

	Univariable analysis			Multivariable analysis		
	HR	95 % CI	P Value	Adjusted HR	95 % CI	p value
Age	1.012	0.984-1.040	0.419			
Gender, male	0.899	0.408-1.978	0.791			
Atrial fibrillation	2.862	1.281-6.391	0.010	0.993	0.353-2.793	0.990
Hypertension	0.849	0.316-2.279	0.745			
Diabetes	0.861	0.322-2.301	0.765			
Coronary artery disease	1.529	0.633-3.691	0.346			
Amiodarone	0.701	0.094-5.240	0.729			
β-blocker	1.529	0.357-6.546	0.567			
NYHA III or IV	4.900	2.222-10.804	<.001	1.551	0.546- 4.407	0.410
Body-mass index	0.874	0.750-1.019	0.085			
LVEDD (mm)	1.038	0.965-1.118	0.317			
Maximal wall thickness (mm)	0.988	0.901-1.183	0.802			
LVEF (%)	0.930	0.901-0.960	<.001	0.977	0.931-1.026	0.350
LVOT Gradient (mmHg)	0.987	0.971-1.003	0.113			
LA diameter (mm)	1.066	1.007-1.128	0.029	1.012	0.934-1.097	0.767
NSVT at 24-hHolter monitoring	0.702	0.286-1.725	0.440			
Syncope	4.630	0.625-3.291	0.134			
Hemoglobin (g/dl)	0.931	0.766-1.131	0.472			
Platelet (×103 µL)	0.997	0.991-1.003	0.331			
WBC (×103 µL)	1.003	0.906-1.111	0.954			
Neutrophil (×103 µL)	1.109	0.920-1.201	0.465			
Lymphocyte (×103 µL)	1.021	0.732-1.426	0.901			
Monocyte (×103 µL)	1.001	0.999-1.002	0.455			
Glucose (mg/dl)	0.996	0.914-1.345	0.295			
Creatinine (mg/dl)	1.037	0.484-2.222	0.925			
Uric acid (mg/dl)	1.047	0.866-1.266	0.635			
Albumin(g/dl)	0.101	0.047-0.214	0.470			
TSH, UI/mL	0.992	0.875-1.124	0.898			
hsCRP (mg/dl)	1.061	1.030-1.092	<.001	1.040	1.006-1.074	0.019
PNI	0.795	0.737-0.857	<.001			
PNI < 40.0	8.453	3.142-22.745	<.001	4.818	1.602-14.490	0.005

Bolded values indicate statistically significant odds ratio.
CI: confidence interval; CRP: C-reactive protein; LA: Left atrium; LVEDD: left ventricular enddiastolic diameter; LVEF: left ventricular ejection fraction;; LVOT:left ventricular outflow tract; NSVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; TSH:thyroid-stimulating hormone; WBC:white blood cell

demonstrated that, despite the relatively benign course of this disease, still 10% of patients progressed to NYHA class III-IV during follow-up [15]. These investigations highlight the need for parameters that could be used to determine HCM patients at risk for HF development before the endstage phase ocur. Several biomarkers, particularly B-type natriuretic peptide (BNP)[16], increased circulating inflammatory markers such as TNF-α [7, 8], IL-6 [17], MCP-1[18], NLR [9] and MHR [6] have recently been shown to be useful in stratifying risk in patients with HCM. Previous studies have shown that several nutritional indicators, including body mass index (BMI), serum albumin, total cholesterol, and total lymphocyte count, predict survival in patients with various cardiovascular diseases. Nakagomi et al. have shown that malnutrition was significantly associated with higher concentrations of inflammatory markers in patients with chronic HF [19]. In patients with HF, however, serum albumin level is influenced by several non-nutritional factors including fluid status, hepatic congestion, renal dysfunction and inflammation. Similarly, BMI is influenced by fluid status, indicating that the measurement of albumin or BMI alone is insufficient as a nutritional risk assessment. In contrast, PNI measured using both serum albumin and lymphocyte count may overcome the shortcomings of each indicator. 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 [20, 21]. PNI has been used as a predictive nutritional marker in patients with various diseases, such as malignancy [22], acute or chronic HF [23, 24], heart failure with preserved ejection fraction (HFpEF) [25], pulmonary embolism (PE) [26], stable coronary artery disease (CAD) [27] and ST segment elevation myocardial infarction (STEMI) [28]. The clinical significance of nutritional risk assessment in patients with HCM has not been well established. To our knowledge, there is no clinical study presenting the association between PNI and adverse cardiac events in HCM in the literature.

There are several potential explanations for the relationship between low PNI and adverse cardiovascular events in patients with HCM. Low PNI is accompanied by hypoalbuminaemia, reflecting malnutrition and inflammation, which are associated with worse HF outcome [29, 30]. In many cases (approximately 50%), HF occurred in the clinical setting of HCM with preserved systolic function presenting a particularly malignant prognosis [31]. Several recent reports have provided data about prognostic value of nutritional status in HF patients with preserved systolic function [18]. In a recent study, importance of PNI was investigated in 1673 patients (52% HFpEF) hospitalised for acute HF[24]. A higher PNI tertile was related to better survival free from allcause death and patients with lower PNI had worst prognosis. Japanese Heart Failure Syndrome with Preserved Ejection Fraction study registered 535 consecutive hospitalised HFpEF patients. This study showed that serum albumin level on admission, was independently related with the composite outcome of all-cause death and heart failure hospitalisation during a median follow-up period[32]. 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. An activated inflammatory state has been reported to be an important factor in the incidence and maintenance of HF. The physiological stress induced by advanced HF results in an increased production of cortisol and a shift in the leukocyte differential toward a decreased percentage of lymphocytes (%L)[33]. 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 neuro-hormonal disorders, decreased caloric intake and impaired perfusion, in patients with HF by combining albumin and lymphocyte levels[33]. In our study, PNI also has a significant positive correlation with serum CRP level, which supports its role in systemic inflammation. This result confirmed that nutritional and immunological situations are important when considering the long-term outcome in patients with HCM. Moreover, we found that lower PNI was independently correlated with a lower left ventricular ejection fraction (LVEF), Its role can be defined as an identifier for high-risk patients who may benefit closely follow-up. In previous studies, some various cutoff values have been detected for PNI. These reports found the optimal cutoff values were 44.5, 45 or 40 [21-23]. According to the ROC curve analysis of the currrent study an optimal cut-off value of 40.0 was obtained.

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 HCM. It remains uncertain how patients with low PNI should be managed. Further investigations are required to evaluate whether nutritional interventions improve clinical outcomes in HCM patients.

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 asses 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. 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.

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 adverse cardiovascular outcomes in HCM patients. Lower PNI

scores were associated with CV deaths in HCM patient. This result confirmed that nutritional and immunological situations are important when considering the long-term outcome in patients with HCM. Our study suggested that the PNI might be useful for risk stratification of HCM patients in clinical practice. Further investigations on independent multicenter cohorts should be performed in order to validate our findings.

Financial & competing interests disclosure

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Ethical conduct of research

This study was performed in keeping with the principles outlined in the Declaration of Helsinki and approved by institutional ethics committee of our hospital.

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