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The value of NT-pro-brain natriuretic peptide and left ventricular ejection fraction for prediction of premature ventricular complexes burden

E. BAYSAL[1], A. USLU[2], A. KÜP[2], M. SAYGI[3], R. DOĞAN[3], L. PAY[4], O. BIRDAL[5], M. OKŞUL[1], G.Y. ARSLAN[6]

[1]Department of Cardiology, Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakır, Turkey
[2]Department of Cardiology, Kartal Koşuyolu Yüksek İhtisas Education and Research Hospital, Istanbul, Turkey
[3]Department of Cardiology, Hisar Intercontinental Hospital, Istanbul, Turkey
[4]Department of Cardiology, Ardahan State Hospital, Ardahan, Turkey
[5]Department of Cardiology, Atatürk University, Erzurum, Turkey
[6]Department of Cardiology, Kepez State Hospital, Antalya, Turkey

Abstract. – OBJECTIVE: We aimed to investigate the relation of NT-pro BNP level and left ventricular ejection fraction with premature ventricular complex burden.

PATIENTS AND METHODS: A total of 94 patients with PVC burden > 5% (age 45.9+12.9 years, 53 males, 41 females) were included in the study. The primary outcome was PVC burden % and main prognostic factors were LVEF% and NT-Pro BNP level. Gender, age, DM, HTN, presence of symptoms, symptoms duration and heart rate were used as adjustment predictor variables. We created four different linear multivariable models to compare performance measures of prognostic factors: Model-1 has gender, age, DM, HTN, symptoms and heart rate, while LVEF has been added in addition to model-1 in model-2. Model-3 included NT-Pro-BNP alongside model-1 variables, while model-4 included both LVEF and NT-Pro-BNP variables in addition to model-1 variables. Accordingly, we compare the performance (R2, likelihood ratio X2) of models.

RESULTS: The median PVC burden was 18% (IQR; 11-27). When model-1 consisting of gender, age, DM, HTN, presence of symptoms, symptom duration and heart rate and model-2 consisting of LVEF in addition to variables of model-1 were compared, it was observed that both LRX2 and R2 values improved (likelihood ratio test *p*-value=0.013). Model-1 compared with model-3 which consisting of NT-pro BNP in addition to variables of model-1, and it was observed that both LRX2 and R2 values improved (likelihood ratio test *p*-value=0.008). However, when compared to model-1, the most significant improvement was observed in both LRX2 and R2 values in model-4 consisting of model-1 plus NT-Pro-BNP and LVEF (likelihood ratio test *p*-value <0.001).

CONCLUSIONS: We determined that NT-pro-BNP levels and LVEF could predict PVC burden in patients. Higher levels of NT-pro-BNP and lower LVEF values were associated with increased PVC burden.

Key Words:
Premature ventricular complex, Left ventricular ejection fraction, NT-pro BNP.

Introduction

In clinical practice, premature ventricular complexes (PVCs) are a frequent arrhythmia[1]. Although patients are usually asymptomatic, they may sometimes present with palpitations, dyspnea, presyncope and fatigue[2]. While PVCs are benign in most cases without structural heart disease, high PVC burden can induce left ventricular (LV) dysfunction and cardiomyopathy or worsen the underlying cardiomyopathy. In the literature was shown that PVC burden is the strongest independent predictor of PVC-induced cardiomyopathy. Although 10% PVC exposure appears to be the minimum threshold for developing left ventricular dysfunction, the risk increases further at 20% PVC exposure[3].

Corresponding Author: Erkan Baysal, MD; e-mail: dr.erkan.baysal@hotmail.com

Three essential pieces of information are required to predict the prognosis of PVC disease: symptom information, PVC exposure, and the presence of structural heart disease. All patients who experience frequent PVCs should get outpatient electrocardiographic monitoring to assess PVC load, the amount and variety of PVC morphologies, and the fluctuation of PVC burden over the day[4]. Although ambulatory Holter monitoring is a necessary method to determine PVC burden, it takes time for patients to reach this examination. The use of transthoracic echocardiography (TTE) for the presence of structural heart disease and ejection fraction is more accessible and can be applied without loss of time. Brain natriuretic peptide (BNP), which can be quickly evaluated for many patients, is a cardiac hormone with diuretic, natriuretic and vasodilator properties. Measurement of concentrations of N-terminal-pro BNP (NT-pro BNP), a more sensitive peptide than plasma B-type natriuretic peptide, is increasingly used to diagnose, predict prognosis, and evaluate therapy in adults with congestive heart failure[5]. The primary stimulus for (NT-pro) BNP secretion is myocardial wall stress. Previous studies[6] suggest that BNP may be a sensitive marker to detect PVC-induced increased ventricular wall stress.

The primary purpose of this study is to investigate whether NT-pro BNP level and ejection fraction measurement with TTE, which are easily accessible and have rapid results, will help in estimating PVC burden.

Patients and Methods

Study Population

In the study, the data of 97 patients who applied to the cardiology outpatient clinic were found to have PVC in 12-lead ECG and were analyzed retrospectively. Patients with a PVC burden > 5% in 24-hour rhythm Holter recordings were included in the study. Patients with previous myocardial infarction, history of CABG, right heart failure, severe valve pathologies, and hypertrophic cardiomyopathy were not included in the study. In addition, patients whose echocardiographic data could not be evaluated accurately, who had rhythm follow-up for less than 12 hours in Holter recordings, and under the age of 18 were also excluded from the study. Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey, Scientific Research Ethics Committee approved the study.

Data Collection

Detailed medical histories and sociodemographic, clinical, and laboratory data of the patients included in the study were obtained retrospectively from patient files. The NT-pro-BNP level was determined by the chemiluminescence (CL) method using I2000 ARCHITECT (Abbott, Chicago, IL, USA). Standard hematological and biochemical parameters were measured using a Beckman Coulter LH 780 machine (Beckman Coulter, Brea, CA, USA).

12-lead, 24-hour, ambulatory ECG (Cardioscan 11 Premier Holter System, DMS, Stateline, NV, USA) devices were used to assess the PVC burden of all study patients. Simultaneous three-channel 24-hour Holter recordings were taken and the recordings were transferred to the computer environment. A digitized Holter program (Cardioscan-11 Holter EKG Systems, DM Software) was used to identify PVCs, then the recordings were visually inspected and unclear recordings areas were excluded. QRS morphology classification was also done automatically by the holter program and obtained after review and manual editing by an experienced technician. Two independent cardiologists then manually reviewed the entire automated interpretation of the recording for all arrhythmic episodes and all unknown traces. A licensed electrophysiologist confirmed the reports. The daily number of PVCs was recorded for each patient. The number of daily QRS complexes was also recorded. PVC burden was defined as the ratio of PVCs to the total number of QRS complexes in a 24-hour recording.

Echocardiographic (Vivid 7®GE Medical System, Horten, Norway) evaluations, left ventricular end-diastolic and end-systolic volumes were measured in apical two- and four-chamber views with modified Simpson's method, and LVEF was obtained. All echocardiographic measurements were made at sinus beats, avoiding the first post-extra systolic beat if possible.

Prognostic factors: LVEF% and NT-Pro BNP level.

Other Adjustment Variables

It was very important that the predictors to be included in the model were clinically and biologically reasonable relationships with PVC burden %. Accordingly, gender, age, DM, HTN, presence of symptoms, symptom duration, and heart rate were used as adjustment predictor variables.

Statistical Modeling

We used the ordinary least regression method to assess the relationships between PVC burden and prognostic factors adjusted for other predictors. The relationship between the prognostic factors and PVC burden was determined using the regression coefficient and 95% confidence interval. We created four different multivariable models to compare performance measures of prognostic factors: Model-1 has gender, age, DM, HTN, symptoms, and heart rate, while LVEF has been added in addition to model-1 in model-2. Model-3 included NT-Pro-BNP alongside model-1 variables, while model-4 included both LVEF and NT-Pro-BNP variables in addition to model-1 variables. Continuous variables included in the model were taken with the restricted cubic spline transformation (3 knots). Accordingly, we compare the performance (R2, likelihood ratio X2) of models. The relative importance of each predictor in the models was estimated with a partial X2 value for each predictor divided by the model's total X2, which estimated the independent contribution of each predictor to the variance of the outcome.

Statistical Analysis

The median and interquartile range were used in presenting numerical variables and the percentage or the number of patients was used in presenting categorical data. The Mann-Whitney U test and the χ^2 statistics were applied to evaluate the baseline and clinical characteristics among patients based on the categorical PVC burden using the median value as a cut-off.

Outcome: PVC burden %. p-values <.05 were considered statistically significant. All statistical analyzes were performed using R-software v.3.5.6 (R statistical software, institute for statistics and mathematics, Vienna, Austria).

Results

A total of 94 patients with PVC burden > 5% (age 45.9+12.9 years, 53 males and 42 females) were included in the study. While 79 (84%) of the patients were symptomatic, the mean duration of symptoms was 31.2 weeks. There were 7 patients with a history of ablation. Other baseline clinical features are summarized in Table I.

Table I. Baseline clinical characteristics.

	Overall group	PVC Burden <18%	PVC Burden ≥18%	p*
Age	45.50 [37.00, 55.00]	49.00 [38.00, 55.00]	44.00 [35.00, 54.50]	0.484
Sex (male)	53 (56.4)	24 (51.1)	29 (61.7)	0.405
presence of symptom	79 (84.0)	44 (93.6)	35 (74.5)	0.024
Symptom duration	12.00 [6.50, 36.00]	24.00 [12.00, 48.00]	12.00 [4.00, 24.00]	0.029
BMI	27.50 [26.00, 30.00]	28.00 [25.10, 30.00]	27.00 [26.00, 29.50]	0.710
HT	20 (21.3)	10 (21.3)	10 (21.3)	1.000
DM	14 (14.9)	9 (19.1)	5 (10.6)	0.385
Smoking	22 (23.4)	8 (17.0)	14 (29.8)	0.223
Previous beta-blocker	67 (71.3)	40 (85.1)	27 (57.4)	0.006
Previous CCB	6 (6.4)	3 (6.4)	3 (6.4)	1.000
Previous Amiodarone	2 (2.1)	2 (4.3)	0 (0.0)	0.475
Previous Propafenon	3 (3.2)	1 (2.1)	2 (4.3)	1.000
Previous ablation	7 (7.4)	1 (2.1)	6 (12.8)	0.116
PVC QRS width	130.00 [120.00, 160.00]	140.00 [130.00, 160.00]	130.00 [120.00, 150.00]	0.055
PVC coupling interval	480.00 [440.00, 520.00]	480.00 [440.00, 530.00]	480.00 [440.00, 520.00]	0.143
Mean heart rate	75.00 [70.00, 84.00]	73.00 [66.50, 79.00]	78.00 [71.50, 84.50]	0.010
LVEDD	4.80 [4.53, 5.10]	4.80 [4.50, 5.10]	4.80 [4.60, 5.00]	0.943
LVESD	3.10 [2.80, 3.40]	3.10 [2.80, 3.40]	3.20 [2.90, 3.40]	0.413
Hgb	13.95 [12.60, 15.00]	13.90 [12.70, 14.80]	14.20 [12.55, 15.35]	0.578
TSH	1.90 [1.40, 2.40]	2.20 [1.70, 2.68]	1.70 [1.25, 2.30]	0.026
CRP	0.34 [0.34, 0.58]	0.34 [0.34, 0.56]	0.34 [0.34, 0.69]	0.244
Nt-Pro-BNP	295.15 [255.12, 485.60]	274.50 [221.00, 314.90]	333.50 [278.70, 605.10]	0.001
LVEF	65.35 [58.47, 67.00]	65.40 [59.70, 67.35]	65.00 [56.20, 67.00]	0.276

PVC: premature ventricular contraction, DM: diabetes mellitus, HT: Hypertension, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, TSH: thyroid stimulating hormone, CRP: C reactive parameter. *Independent *t*-Student.

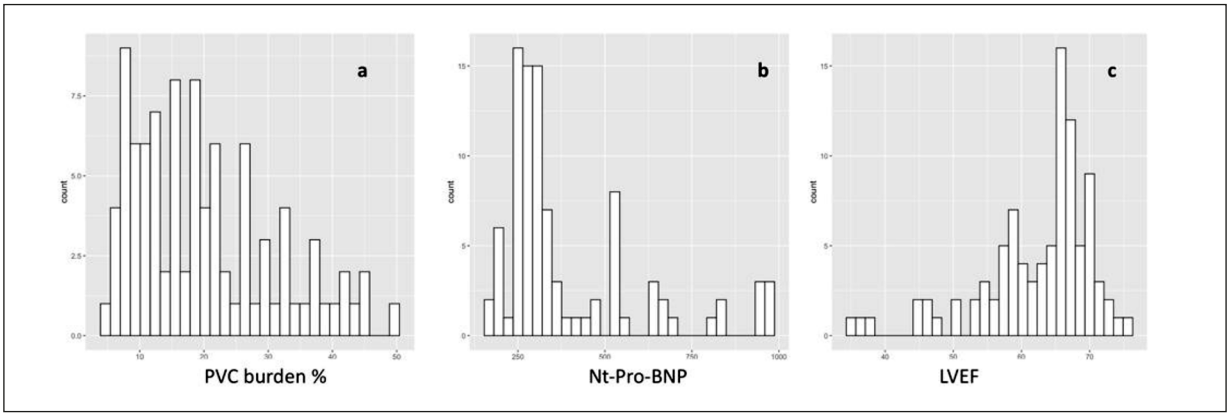

Figure 1. Histogram plot for distribution of PVC-burden (**a**), Nt-Pro-BNP (**b**) and LVEF (**c**).

In the 24-hour continuous heart rhythm monitoring of the patients included in the study, the median PVC burden was 18% (IQR; 11-27) (Figure 1a). In addition, 9.5% (n=9) of the study population had LVEF <50% (Figure 1b), while median NT-Pro-BNP levels were 301 pg/dl (261-522) (Figure 1c). When model-1 consisting of gender, age, DM, HTN, presence of symptoms, symptom duration, and heart rate, and model-2 consisting of LVEF in addition to variables of model-1 were compared, it was observed that both LRX2 and R2 values improved (likelihood ratio test *p*-value=0.013). Model-1 compared with model-3 which consists of NT-pro BNP in addition to variables of model-1, and it was observed that both LRX2 and R2 values improved (likelihood ratio test *p*-value=0.008). However, when compared to model-1, the most significant improvement was observed in both LRX2 and R2 values in model-4 consisting of model-1 plus NT-Pro-BNP and LVEF (likelihood ratio test *p*-value <0.001) (Table II).

Therefore, model 4 was considered to be the most useful model. Figure 2 shows how each of the variables included in model 4 contributes to the variation in PVC burden (%). LVEF and NT-Pro-BNP alone explain approximately 67% of the variation in PVC burden (%). In Figure 3, the relationship of LVEF and NT-Pro-BNP with PVC burden (%) is shown in the partial effect plot.

Discussion

In this study we determined that NT-pro-BNP levels and LVEF could predict PVC burden in patients. Higher levels of NT-pro-BNP and lower LVEF values were associated with increased PVC burden.

PVC is a common arrhythmia seen in 1-4%

Table II. Multivariable linear regression models for predictions of PVC burden %.

	Model-1	Model-2	Model-3	Model-4
Age (from 37 to 55)	1.84 (-1.43, 5.11)	0.90 (-2.36, 4.17)	1.82 (-1.24, 4.89)	0.98 (-2.09, 4.05)
Sex (male)	0.94 (-4.05,5.93)	2.57 (-2.38, 7.54)	0.90 (-3.78, 5.58)	2.39 (-2.27, 7.06)
DM	-1.87 (-8.74, 4.99)	-1.72 (-8.35, 4.93)	-2.41 (-8.87, 4.06)	-2.25 (-8.53, 0.95)
HT	-3.18 (-9.24, 2.86)	-2.63 (-8.51, 3.23)	-3.32 (-9.01, 2.36)	-2.79 (-8.32, 2.74)
Presence of symptoms	-3.32 (-10.2, 3.57)	-3.66 (-10.3, 3.01)	-3.87 (-10.3, 2.59)	-4.15 (-10.4, 2.14)
Symptoms duration (from 6.5 to 36)	-4.76 (-9.44, -0.08)	-5.06 (-9.64, -0.47)	-3.19 (-7.79, 1.40)	-3.58 (-8.11, 0.95)
Heart rate (from 70 to 84)	4.71 (1.27, 8.14)	3.01 (-0.54, 6.57)	3.99 (0.75, 7.24)	2.48 (-0.88, 5.84)
LVEF (from 58 to 67)	-	-4.32 (-7.63, -1.00)	-	-3.91 (-7.04, -0.78)
NT-Pro-BNP (from 262 to 522)	-	-	5.69 (2.32, 9.06)	5.32 (2.05, 8.60)
Intercept	17.4	40.7	6.90	29.9
Model performances	20.6	29.3	34.9	43.3
LR X2 R2	0.197	0.268	0.310	0.369

PVC: premature ventricular contraction, DM: diabetes mellitus, HTN: Hypertension, LVEF: left ventricular ejection fraction, LR X2: likelihood ratio Chi-square.

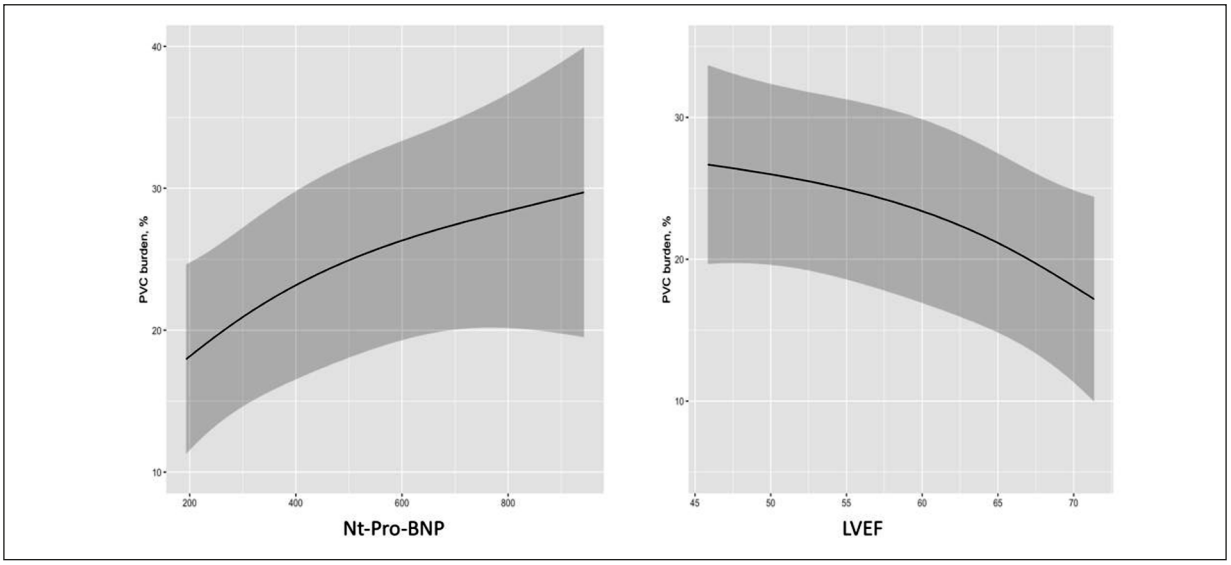

Figure 2. Partial effect plot for LVEF and NT-proBNP in predictions of PVC burden (%).

of standard 12-lead ECGs of the general population7. In 24-48-hour, rhythm Holter monitoring, the frequency of PVC varies between 40% and 75%[8]. Studies[9,10] conducted in people without heart disease have shown that death, cardiovascular death, ischemic heart disease, and heart failure were found to be higher in patients with PVC detected in rhythm Holter monitoring than those without. However, it was found that PVCs are mostly associated with a good prognosis[11]. Studies[7,11-14] have shown that the conditions associated with poor prognosis are underlying structural, ischemic, and electrical abnormalities, PVC burden over 10% in rhythm holter monitoring, complex PVCs such as couplet, triplet, or non-sustained VT, multifocal PVCs, increase in PVC burden with exercise, PVCs originating from areas outside the outflow tract (LVOT, RVOT), R on T phenomenon and PVCs with wide QRS.

Studies[15,16] have shown that the poor prognosis of PVCs is caused by left ventricular dilatation and deterioration in left ventricular systolic functions.

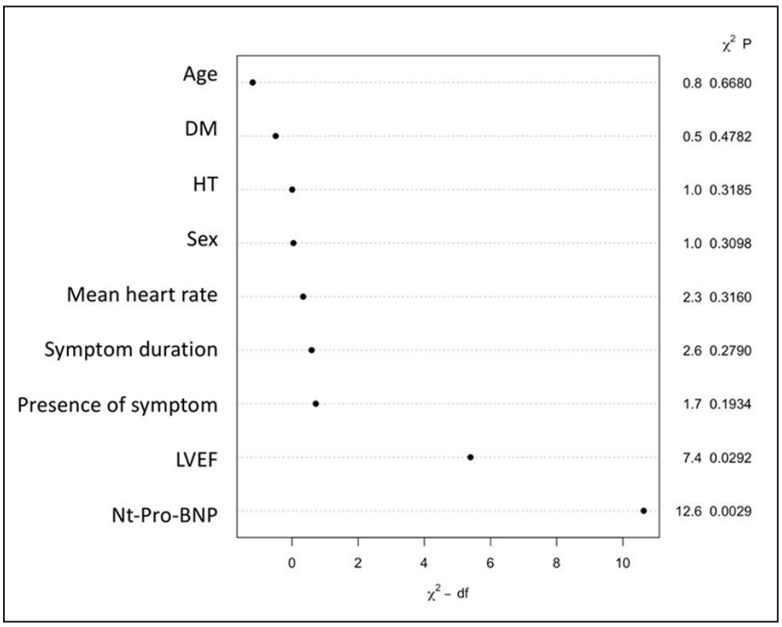

Figure 3. The rank of variable importance in the multivariable model-4.

This clinical condition has been named PVC- induced cardiomyopathy[17]. On the other hand, the incidence of PVC frequently increases in case of low LVEF, and this situation can create difficulties in distinguishing which triggers the other. PVC-induced cardiomyopathy constitutes the most important patient group in terms of antiarrhythmic therapy and catheter ablation[7]. It has been shown that the most important risk factor in PVC- induced cardiomyopathy is PVC burden and >10% PVC burden was found to be significant in terms of the risk of developing cardiomyopathy[7,11,13].

Rhythm holter monitoring is used to determine the PVC load in a patient with PVC detected in the ECG. However, compared to ECG, echocardiography, and laboratory tests, Holter monitoring can cause significant delays in the diagnosis and treatment process in terms of accessibility. In a study[18] conducted in Europe it was determined that an average of 39 days elapsed between the patient's admission to the hospital and seeing the holter result and starting the treatment. In addition, depending on the fact that the daily PVC load is affected by many factors, Holter monitoring may need to be extended up to 6 days to determine the actual PVC load[19]. Therefore, in a patient with PVC on ECG, it seems important to use easily accessible echocardiography and clinical predictive laboratory parameters to correlate with Holter in the estimation of PVC burden in the period until Holter monitoring. In addition, echocardiography is an important diagnostic method in which findings of structural heart diseases, myocarditis, and ischemic heart diseases can be seen, as well as PVC-induced cardiomyopathy, which is one of the important prognostic indicators of PVC[20,21].

We considered BNP and NT-pro-BNP to be predictors together with LVEF since they are an important indicator of mortality in asymptomatic left ventricular dysfunction independent of LVEF in terms of showing deterioration in myocardial functions[22]. BNP and NT-pro-BNP are released from the ventricle in cases of increased myocardial wall tension and hypervolemia[22]. Previous studies[23,24] have shown that high BNP and NT-pro-BNP levels are associated with high mortality in both patients with heart failure and patients with asymptomatic left ventricular dysfunction. In some studies, increased BNP and NT-pro-BNP levels were found to be associated with increased ventricular ectopia[25,26]. As an explanation for this relationship, it is thought that the increase in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (PCWP) following PVC will increase the left ventricular filling pressures and consequently the amount of BNP released from the left ventricle[26]. In our study, we found NT-pro-BNP to be a very strong parameter in terms of predicting PVC load. We also found LVEF to be the second strongest predictor after NT-pro-BNP. We found that variables such as age, gender, DM, HT, symptom duration, presence of symptoms, and heart rate, which we took as other enhancing parameters, did not significantly contribute to the improvement of the model.

In this study, we determined that by evaluating together LVEF and NT-pro-BNP detected by simple and easily accessible echocardiography and laboratory tests, it may be used to predict PVC burden, before Holter monitoring which can take time in terms of access and sometimes requires a long examination time in symptomatic or asymptomatic patients with PVC detected on ECG.

Limitations

The most important limitations are the retrospective nature of the study and the small sample size. Our patient population was a relatively small population of 93 patients. Our findings need to be investigated with larger- scale studies. In addition, our findings cannot be generalized to the group of patients with a PVC load of <5%, since patients with a PVC load of <5% were not included in our study.

Conclusions

LVEF and NT-pro-BNP may be beneficial in predicting and prognostic evaluation of PVC burden in the period before rhythm Holter monitoring.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

For this retrospective study, formal consent is not required.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The research protocol was reviewed and approved by the Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee.

Authors' Contribution

The study's conception and design were contributed by EB, AU, and AK. The first draft of the manuscript was written by EB, LP, MS, RD. Material preparation, data collection, and analysis was performed by EB, LP, OB, MO and GYA. The final versions of the manuscript were revised by EB, MS, AU, GYA and AK. The final manuscript was read and approved by all authors.

ORCID ID

EB: 0000-0001-5151-5133; AU: 0000-0002-7841-7952; AK: 0000-0002-5969-8402; MS:0000-0002-7258-2797; RD:0000-0003-3563-8779; LP:0000-0002-7491-8119; OB: 0000-0002-0667-2516; MO:0000-0002-4759-4868; GYA: 0000-0002-0114-7448.

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