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Prognostic Significance of High-Sensitivity Troponin T in Nonischemic Heart Failure with Reduced Ejection Fraction

İskemik olmayan düşük ejeksiyon fraksiyonlu kalp yetersizliğinde yüksek duyarlılıklı troponin T'nin prognostik önemi

ABSTRACT

Objective: Cardiac biomarkers can help diagnose and predict heart failure prognosis. High-sensitivity troponin T has frequently been investigated in ischemic heart failure studies. However, the relation between high-sensitivity troponin T and mortality in nonischemic heart failure and its level indicating poor prognosis remain unclear. This study aimed to show whether high-sensitivity troponin T is a predictor of all-cause mortality and the cut-off value for high-sensitivity troponin T in patients with nonischemic heart failure with reduced ejection fraction.

Methods: We included 249 nonischemic heart failure patients with left ventricular ejection fraction ≤ 40%, age ≥ 18 years, and high-sensitivity troponin T level known.

Results: Of the patients, 59.8% were male, 73.5% were New York Heart Association I or II, and the median age was 64. High-sensitivity troponin T value of the patients was 18 ng/L [interquartile range, 10-34]. The cut-off value of high-sensitivity troponin T for all-cause mortality was 21.5 ng/L, with 72.6% sensitivity and 69.9% specificity (area under the curve: 0.760, 95% CI: 0.692-0.828, $P < 0.001$). Patients were compared according to the 21.5 ng/L high-sensitivity troponin T cut-off value. At 30-month follow-up, all-cause mortality was 29.3%. According to the Kaplan–Meier analysis, the mortality rate was 14% in the high-sensitivity troponin T < 21.5 ng/L group, while the mortality rate was 50% in the high-sensitivity troponin T ≥ 21.5 ng/L group ($P < 0.001$, log-rank test). Baseline high-sensitivity troponin T was independently associated with all-cause mortality in nonischemic heart failure with reduced ejection fraction when adjusted for estimated glomerular filtration rate, hemoglobin, N-terminal pro-brain natriuretic peptide, body mass index, and left atrial diameter (hazard ratio: 1.012, 95% confidence interval: 1.003-1.020, $P=0.005$).

Conclusion: The high-sensitivity troponin T cut-off value was 21.5 ng/L to predict a worse prognosis in nonischemic heart failure with reduced ejection fraction. There was an independent association between high-sensitivity troponin T and all-cause mortality.

Keywords: All-cause mortality, heart failure, high-sensitivity troponin T, nonischemic, reduced ejection fraction.

ÖZET

Amaç: Kardiyak biyobelirteçler, kalp yetersizliğinin (KY) teşhis edilmesine ve prognozunun tahmin edilmesine yardımcı olabilir. Yüksek duyarlıklı troponin T (ydTnT) iskemik KY çalışmalarında daha sık araştırılmaktadır. Ancak iskemik olmayan KY'de ydTnT ile mortalite arasındaki ilişki ve hangi değerlerin kullanılması gerektiği belirsizliğini koruyor. Bu çalışma, iskemik olmayan düşük ejeksiyon fraksiyonlu KY hastalarında (DEFKY), ydTnT'nin tüm nedenlere bağlı mortalitenin bir öngördürücüsü olup olmadığını ve hsTnT'nin eşik değerini göstermeyi amaçlamıştır.

Yöntem: Sol ventrikül ejeksiyon fraksiyonu (LVEF) ≤ %40, yaşı ≥18 olan ve ydTnT düzeyi bilinen 249 iskemik olmayan KY hastasını çalışmaya dahil ettik.

Bulgular: Hastaların %59,8'i erkek, %73,5'i NYHA I veya II ve medyan yaş 64'tü. Hastaların ydTnT değeri 18 ng/L [IQR, 10-34] idi. ydTnT'nin tüm nedenlere bağlı mortalite için eşik değeri %72,6 duyarlılık ve %69,9 özgüllük ile 21.5 ng/L idi (eğrinin altındaki alan: 0,760, %95 GA: 0,692-0,828, $P < 0,001$). Hastalar 21.5 ng/L ydTnT cut-off değerine göre karşılaştırıldı. 30 aylık takipte tüm nedenlere bağlı mortalite %29.3 idi. Kaplan-Meier analizine göre ydTnT < 21,5 ng/L grubunda mortalite oranı %14 iken ydTnT ≥ 21,5 ng/L grubunda mortalite

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KLİNİK ÇALIŞMA

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oranı %50 idi (P < 0,001, log-rank testi). Bazal ydTnT, eGFR, hemoglobin, NT-proBNP, BMI ve sol atriyal çap için ayarlandığında iskemik olmayan DEFKY'de tüm nedenlere bağlı mortalite ile bağımsız olarak ilişkiliydi (HR: 1,012, %95 CI: 1,003-1,020, P=0,005).

Sonuç: İskemik olmayan DEFKY'de daha kötü bir prognozu öngörmek için ydTnT eşik değeri 21,5 ng/L idi. ydTnT ile tüm nedenlere bağlı mortalite arasında bağımsız bir ilişki vardı.

Anahtar Kelimeler: Düşük ejeksiyon fraksiyonu, iskemik olmayan, kalp yetersizliği, tüm nedenlere bağlı ölüm, yüksek duyarlıklı troponin T.

Despite advanced treatment approaches, heart failure (HF) is still an important cause of morbidity and mortality. Biomarkers can help diagnose HF, predict prognosis, and evaluate treatment response. The prognostic importance of natriuretic peptides in HF well known. High-sensitivity troponin T (hsTnT) is another cardiac marker that can be assesed rapidly.[1-3] Among the several mechanisms associated with troponin increase in HF, the most likely mechanism is subendocardial ischemia with or without obstructive coronary arteries.[4] In addition, upregulation of renin-angiotensin-aldosterone levels in HF results in permanent cell damage and death with troponin increase.[5]

The prognostic value of cardiac troponins was emphasized first in acute HF and then in chronic HF.[6,7] In a meta-analysis, hsTnT was shown to independently predict all-cause death, cardiovascular mortality, and hospitalization in a prognostic model of known risk markers, including N-terminal pro-brain natriuretic peptide (NT-proBNP).[7] In this study, which included ischemic and nonischemic patients, the hsTnT cut-off value for all outcomes was 18 ng/L. In another study conducted in 2021, hsTnT was evaluated separately in ischemic and nonischemic HF.[8] In ischemic HF, the predictive hs-cTnT cut-off value for HF hospitalization and death from all causes was 0.0275 ng/mL. But, this value was not detected in nonischemic HF. It remains unclear whether hsTnT is associated with mortality in nonischemic HF and which values should be used.

The aim of our study was to show whether hsTnT is a predictor of death from all causes in patients with nonischemic heart failure with reduced ejection fraction (HFrEF).and which cut-off value for hsTnT should be used to predict mortality.

Materials and Methods

Study Population

A total of 520 patients followed in the HF outpatient clinic between 2015 and 2020 were evaluated. The study included 249 nonischemic HF patients aged ≥ 18 years with a left ventricular ejection fraction (LVEF) ≤ 40% and a known hsTnT level. Approval was obtained from the local ethics committee for the study. The diagnosis of HF was evaluated according to the guidelines.[9] hsTnT was measured with Cobas e 411 analyzer and Roche's Elecsys assay. The 99th percentile upper reference limit is 14 ng/L. Nonischemic HF was defined as no history of myocardial infarction and no significant obstructive coronary heart disease on coronary angiography. To reduce the effects of troponin elevation due to renal failure on the results, patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 were excluded from the study. In addition, patients with severe valve disease, acute coronary syndrome, acute cerebral event, acute pulmonary embolism, and septic state were excluded from the study. Demographic characteristics of the patients, hsTnT and other laboratory results, electrocardiogram, echocardiography findings, and medical treatment used were recorded from the hospital database.

Statistical Analysis

Statistical analyses were performed using a Statistical Package for the Social Sciences 22.0 software (IBM Corp, Armonk, NY, USA). The Kolmogorov–Smirnov test was used as a normality test. Normally distributed data are given with mean value and standard deviation, and nonnormally distributed data are given as median and interquartile ranges (IQR). Spearman's rho test was used for variables associated with hsTnT. The groups were compared with the Student's t-test or the Mann–Whitney U-test according to the normality test. Categorical data were given as percentages and compared with the Chi-square test. Log-transformed values were used to reduce the effect of extreme values for NT-proBNP values. The hsTnT cut-off value, sensitivity, and specificity for death from all causes were evaluated by receiver operating characteristic (ROC) analysis. In addition, positive and negative predictive values were determined for this cut-off value. The patients were divided into 2 groups according to the hsTnT cut-off value and compared. The hsTnT groups were compared in terms of survival with the Kaplan–Meier survival analysis and evaluated with the log-rank test. The Cox regression analysis was used for predictors of all-cause mortality. In the univariate regression analysis of the Cox regression model, those with significant P values were included in the multivariate regression analysis. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). A P value of < 0.05 was considered statistically significant.

Results

The median age of 249 patients was 64 years, LVEF 30% [IQR, 25-35], 59.8% male and 40.2% female. Most patients were in New York Heart Association (NYHA) I or II functional class (73.5%), while 26.5% were NYHA III or IV. Around 31.3% of patients had diabetes, 49.4% had hypertension, and 15.5% had chronic kidney disease. The median hsTnT value of the patients was 18 ng/L [IQR, 10-34]. The hsTnT values were median 17 ng/L in women [IQR, 10-32.5] and 19 ng/L in men [IQR, 10.5-35] (P=0.24). The hsTnT levels were significantly negatively correlated with albumin, hemoglobin, total cholesterol, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACE-I/ARB), and aldosterone antagonist use, while positively correlated with NYHA class (Table 1).

The area under the curve (AUC) of ROC for all-cause mortality of hsTnT was 0.760 (95% CI: 0.692-0.828, P < 0.001) (Figure 1). The best cut-off value for hsTnT was 21.5 ng/L in deaths from all

Table 1. Univariate Correlations for hsTnT

Variable	Correlation Coefficient (Spearman's rho)	*P*
NYHA	0.220	<0.001
Albumin	–0.417	<0.001
Hemoglobin	–0.277	<0.001
Total cholesterol	–0.231	<0.001
ACE-I/ARB	–0.233	<0.001
Aldosterone antagonist	–0.170	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; hsTnT, High-sensitivity troponin T; NYHA, New York Heart Association.

causes. This cut-off value had 72.6% sensitivity, 69.9% specificity, 50% positive predictive value, and 86% negative predictive value. The cut-off value of hsTnT was 19.5 ng/L in women with 78% sensitivity and 77% specificity (AUC: 0784, 95% CI: 0.670-0.899, $P < 0.001$), while the cut-off value was 22.5 ng/L in men with 69% sensitivity and 70% specificity (AUC: 738, 95% CI: 0.651-0.824, $P < 0.001$).

The patients were divided into 2 groups according to the hsTnT value, and the groups below and above 21.5 ng/L were compared (Table 2). The group with hsTnT ≥ 21.5 ng/L was significantly older ($P=0.005$), had a lower body mass index (BMI) ($P=0.029$), lower diastolic blood pressure ($P=0.032$), higher heart rate ($P=0.035$), and atrial fibrillation rate was higher ($P=0.004$). While the frequency of chronic kidney disease and the ratio of NYHA class III or IV patients were higher in the

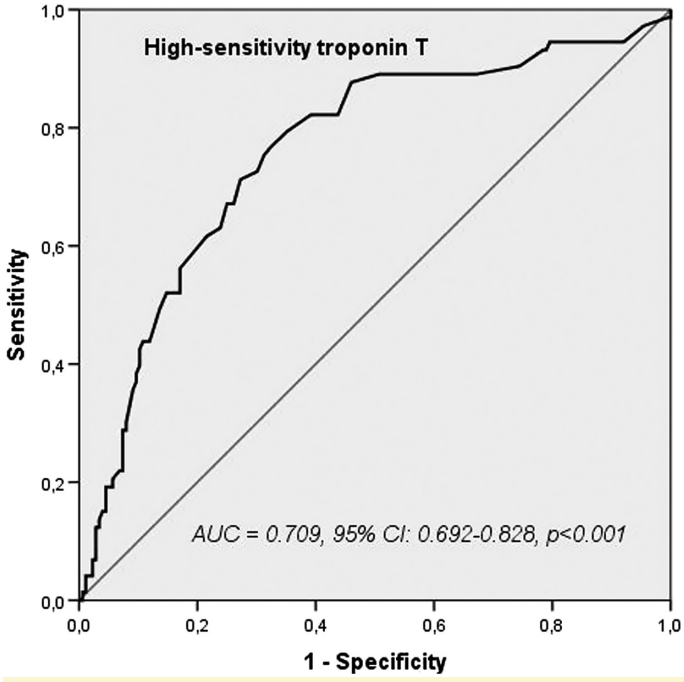

Figure 1. ROC curve for high-sensitivity troponin T to predict the all-cause mortality in nonischemic heart failure.

Table 2. Baseline Characteristics of Patients with Nonischemic Heart Failure According to hsTnT

Characteristics	hsTnT < 21.5 ng/L (n=143)	hsTnT ≥ 21.5 ng/L (n=106)	*P*
hsTnT (ng/L)	11 (7-16)	35.5 (27.7-64)	<0.001
Age (years)	62 (50-69)	66 (53-76)	0.005
Male, n (%)	80 (55.9)	69 (65.1)	0.145
Female, n (%)	63 (44.1)	37 (34.9)	
BMI (kg/m²)	27.5 (24.1-31.5)	25.9 (23.4-28.5)	0.029
HF duration (months)	12 (2-48)	18.5 (2-56)	0.347
Medical history			
Diabetes, n (%)	43 (30.1)	35 (33)	0.62
Hypertension, n (%)	71 (49.7)	52 (49.1)	0.926
Hyperlipidemia, n (%)*	38 (26.6)	20 (18.9)	0.155
Chronic kidney disease, n (%)	10 (7)	26 (24.5)	<0.001
Chronic obstructive pulmonary disease, n (%)	23 (16.1)	22 (20.8)	0.344
Medication			
ACE-I/ARB, n (%)	121 (84.6)	71 (67)	0.001
Beta-blockers, n (%)	129 (90.2)	97 (91.5)	0.726
Aldosterone antagonist, n (%)	112 (78.3)	68 (64.2)	0.013
Loop diuretics, n (%)	92 (64.3)	80 (75.5)	0.06
ICD, n (%)	18 (12.6)	9 (8.5)	0.61
CRT, n (%)	5 (3.5)	4 (3.8)	
Physical findings			
Systolic BP (mm Hg)	110 (100-120)	110 (100-120)	0.153
Diastolic BP (mm Hg)	70 (60-70)	60 (60-70)	0.032
Heart rate (b.p.m)	76 (65-89)	80 (69-95)	0.035
Atrial fibrillation, n (%)	31 (21.7)	42 (39.6)	0.004
NYHA I, n (%)	55 (38.5)	22 (20.8)	0.01
NYHA II, n (%)	57 (39.9)	49 (46.2)	
NYHA III or IV, n (%)	31 (21.7)	35 (33)	
Echocardiographic data			
LVEF, %	30 (25-35)	30 (20-35)	0.1
LV EDD (mm)	57 (53-61)	59 (53-66)	0.119
LV ESD (mm)	46 (42-52)	50 (42-56)	0.055

(*Continued*)

Table 2. Baseline Characteristics of Patients with Nonischemic Heart Failure According to hsTnT (*Continued*)

Characteristics	hsTnT < 21.5 ng/L (n=143)	hsTnT ≥ 21.5 ng/L (n=106)	*P*
PAB (mm Hg)	36 (30-45)	42 (33-55)	0.009
LA diameter (mm)	43 (39-48)	47 (43-52)	<0.001
Laboratory data			
Creatinin (mg/dL)	1.04 (0.91-1.16)	1.24 (0.97-1.6)	<0.001
eGFR (mL/min/1.73 m²)*	72 (55-85)	53 (39-76)	<0.001
Total cholesterol (mg/dL)	184 (147-221)	159 (130-197)	<0.001
Sodium (mmol/L)	139 (137-141)	139 (136-141)	0.847
Albumin (g/dL)	4.4 (4.1-4.7)	4 (3.6-4.3)	<0.001
Hemoglobin (g/dL)	13.3 (±1.7)	12.4 (±2)	0.001
NT-proBNP (ng/L)	1209 (430-2594)	3290 (1865-7443)	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; b.p.m., beats per minute; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; hsTnT, high-sensitivity troponin T; HF, heart failure; ICD, implantable cardioverter defibrillator; LA, left atrium; LV EDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LV ESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro-brain natriuretic peptide NYHA, New York Heart Association; PAB, pulmonary artery pressure.
Normally distributed data were expressed as means with standard deviations and nonnormally distributed data were expressed as medians with interquartile ranges [25%-75%]. The *P* values, between the groups were determined using the Mann–Whitney *U*-test, Student's t-test, or the χ^2 test.
*eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

group with hsTnT ≥ 21.5 ng /L ($P < 0.001$, $P=0.01$, respectively), the rate of ACE-I/ARB and aldosterone antagonist use was lower ($P=0.001$, $P=0.013$, respectively). In addition, pulmonary artery pressure, left atrium diameter, creatinine, and NT-proBNP were higher in this group ($P=0.009$, $P < 0.001$, $P < 0.001$, $P < 0.001$, respectively). The eGFR, total cholesterol, albumin, and hemoglobin were lower in the group with hsTnT ≥ 21.5 ng/L (all, $P < 0.001$).

At a median follow-up of 30 months [IQR, 24-35], 73 patients (29.3%) died from all causes. The relationship between mortality and hsTnT groups was evaluated by Kaplan–Meier analysis. While the mortality rate was 14% in the hsTnT < 21.5 ng/L group, it was significantly higher (50%) in patients with hsTnT ≥ 21.5 ng/L ($P < 0.001$, log-rank test) (Figure 2).

The Cox regression analysis adjusted for eGFR, hemoglobin, NT-proBNP, BMI, and left atrial diameter showed that baseline hsTnT was independently associated with all-cause mortality in nonischemic HF (HR:1.012, 95% CI:1.003-1.020, $P=0.005$) (Table 3).

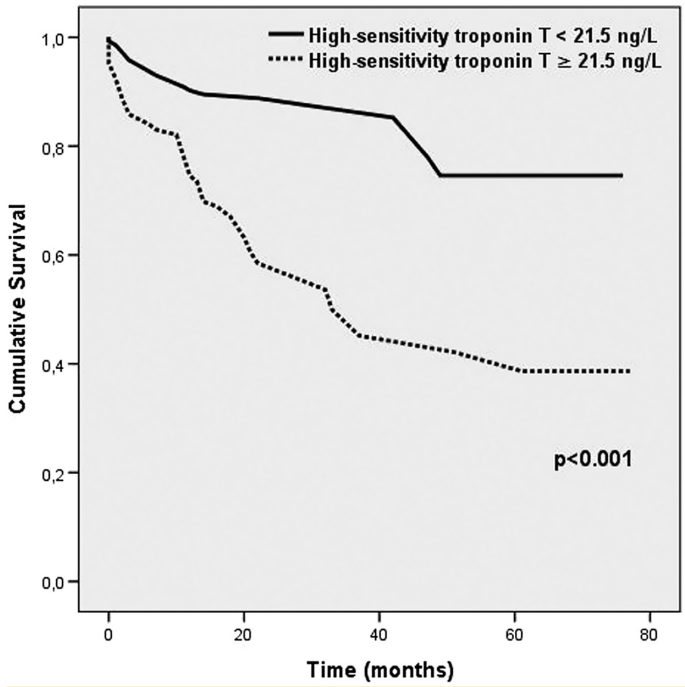

Figure 2. Kaplan–Meier curves for time to all-cause mortality among 249 patients with nonischemic heart failure according to 2 groups of high-sensitivity troponin T.

Discussion

Our study evaluated the prognostic significance of hsTnT in nonischemic HFrEF. First, the hsTnT threshold was 21.5 ng/L and had a sensitivity of 72.6% and a specificity of 69.9% to predict a worse prognosis. Second, hsTnT is associated with a significantly increased risk of mortality (HR: 1.012, 95% CI: 1.003-1.020, $P=0.005$). Thus, in addition to previously known markers, hsTnT makes it possible to predict high-risk patients in nonischemic HFrEF patients.

Biomarkers are important both in the follow-up of HF patients and in determining the risk of HF. The recently published article on the importance of HF biomarkers has provided increasing evidence about the role and potential of troponin in the follow-up of HF patients.[10] Troponin is a recommended biomarker that aids in the diagnosis, follow-up, treatment, and outcome prediction of HF.[11] Although the mechanism of troponin elevation in HF is not clearly known, subendocardial ischemia due to supply–demand imbalance plays an important role.[12] The hsTnT above the upper reference limit is a test with high sensitivity and specificity that detects myocardial damage very early.[13] Also, hsTnT may show minor myocardial injury earlier than NT-proBNP. Therefore, it may help as a in more accurate assessment of the prognosis in HF.[14,15] The fact that NT-proBNP values were higher in the group with high hsTnT in our study supports this suggestion ($P < 0.001$).

Troponin is the best-known cardiac biomarker for detecting myocardial injury.[16,17] The new high-sensitivity troponin (hsTn) is a biomarker suitable for prognostic evaluation as even very low

Table 3. Univariate and Multivariate Analysis for All-Cause Mortality

	Univariate Analysis		Multivariate Analysis	
Variables	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P***
hsTnT	1.012 (1.007-1.017)	<0.001	1.012 (1.003-1.020)	0.005
eGFR	0.983 (0.973-0.994)	0.002	0.995 (0.981-1.010)	0.528
Hemoglobin	0.732 (0.649-0.826)	<0.001	0.805 (0.681-0.951)	0.011
NT-proBNP	4.910 (2.891-8.338)	<0.001	1.543 (0.770-3.094)	0.222
Heart rate	1.009 (1.004-1.013)	0.056		
BMI	0.912 (0.864-0.963)	0.001	0.885 (0.817-0.960)	0.003
Left atrium diameter	1.054 (1.028-1.081)	<0.001	1.036 (0.995-1.079)	0.084

eGFR, estimated glomerular filtration rate; hsTnT, High sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; BMI, body mass index. Values for NT-proBNP were log-transformed before analysis.

levels can be measured.[18] However, the prognostic value as well as the pathophysiology of increased hsTn levels, are not fully understood yet. Also, cut-off levels are always test-specific and not uniformly defined.

The hsTnT levels were directly related to NYHA classes.[19] As the severity of HF increased, hsTnT levels also increased. Similarly, in our study, the ratio of NYHA class III-IV and NT-proBNP levels indicating more advanced HF were higher in the hsTnT ≥ 21.5 ng/L group. The hsTnT appears to be a good prognostic marker besides the severity of HF.

Many large-scale studies have investigated the prognostic significance of troponins in chronic HF. In a large study of 4053 patients, 10.4% of patients had elevated troponin and correlated with NYHA. It was also related with long-term mortality.[20] In this study, troponin T levels were related with an increased risk of mortality (HR: 2.08, 95% CI: 1.72-2.52) and first hospitalization (HR: 1.55, 95% CI: 1.25-1.93) in HF. Similarly, increased hsTn had a twofold increased risk of 5-year mortality in addition to other risk factors.[21] Increased hsTnT has been shown to be a predictor of readmission, mortality, and cardiovascular events in HF.[22-24] Cut-off values of high-sensitivity cardiac troponin I have been reported to be 2.6 ng/L in women and 4.2 ng/L in men.[25] The cut-off value was 21.5 ng/L in the study population, while the cut-off value was lower in women. The cut-off value of hsTnT was 19.5ng/L in women and 22.5 ng/L in men in our study.

Study, which examined different biomarkers to predict adverse outcomes after discharge in acute HF, suggested that hsTn can be used for risk stratification in the admission and discharge of patients with acute HF.[26] In a meta-analysis of 10 studies, 11 of which reported data from a cohort and 9289 patients, 60% had ischemic HF and 85% had LVEF <40%.[7] In this analysis, hsTnT was found to be an important independent predictor of adverse outcome in chronic HF. At 2.4 years of follow-up, hsTnT was associated with deaths from all causes (HR: 1.48, 95% CI: 1.41-1.55), cardiovascular deaths (HR: 1.40, 95% CI: 1.33-1.48), and hospitalization (HR: 1.42, 95% CI: 1.36-1.49) as well, independent of ischemic versus nonischemic etiology ($P < 0.001$). Cut-off values of 18 ng/L from the AUC were independent prognostic values for all 3 endpoints in both ischemic and nonischemic etiology. Thus, the prognostic relationship of hsTnT has been reported to be independent of the etiology of HF.[7] A previous study, that patients with hsTnT levels > 0.014 ng/mL had a higher rate of readmission (23.7%) than those with hsTnT levels < 0.014 ng/mL (7.0%) ($P < 0.05$). In addition, the hsTnT threshold value of 0.0275 ng/mL was calculated with 76.9% sensitivity and 63.5% specificity in the prediction of hospitalization and death in ischemic HF (AUC=0.709, 95% CI: 0.561-0.856, $P < 0.05$). The hsTnT adjusted for different variables was independently associated with hospitalization and all-cause mortality in HF ($P < 0.05$). However, this was not significant in nonischemic HF.[8] It was seen that there are not enough studies on the prognostic importance and cut-off value of hsTnT in nonischemic HF. In our study, baseline hsTnT was independently associated with all-cause mortality in nonischemic HFrEF (HR: 1.012, 95% CI:1.003-1.020, $P=0.005$). And the hsTnT cut-off value of 21.5 ng/L was found to predict all-cause mortality.

Limitations

The data was retrospectively obtained from the follow-up records of a study population in a single HF outpatient clinic, so the results may not generalized to other HF populations. However, we think that it can be a catalyst that sparks ideas for future studies. Due to the retrospective design of the study, the number of patients was limited. Only the basal hsTnT values of the patients at the outpatient admission were evaluated. Temporal hsTnT changes were not evaluated during follow-up. It does not provide information for HF patients with non-reduced LVEF, as only patients with LVEF ≤ 40% were included in the study. Therefore, prospective studies are needed for HF with preserved LVEF or mildly reduced LEVF.

Conclusion

In conclusion, hsTnT has prognostic importance in nonischemic HFrEF just as it does in ischemic HF. Thus, hsTnT may help identify high-risk nonischemic HFrEF patients and in arranging further supportive treatment. With the use of prognostic biomarkers, outcomes in HF patients can be improved further.

Ethics Committee Approval: The study complies with the Declaration of Helsinki and was approved by ethics committee of Antalya Training and Research Hospital on 31/03/2022 with the decision numbered 7/22.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.M.Y.Ö., A.G.; Design – G.M.Y.Ö., A.G.; Supervision – G.M.Y.Ö., A.G.; Funding – G.M.Y.Ö., A.G.; Materials – G.M.Y.Ö., A.G.; Data Collection and/or Processing – G.M.Y.Ö., A.G.; Analysis and/or Interpretation – G.M.Y.Ö., A.G.; Literature Review – G.M.Y.Ö.; Writing – G.M.Y.Ö.; Critical Review – G.M.Y.Ö., A.G.

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