ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Can Glypican-6 Levels Be Used to Determine Right Ventricular Remodeling After Non-ST Segment Elevation Myocardial Infarction?

Glypican-6 Düzeyleri ST Elevasyonu Olmayan Miyokard Enfarktüsü Sonrası Sağ Ventrikül Yeniden Şekillenmesinin Belirlenmesinde Kullanılabilir Mi?

ABSTRACT

Objective: Myocardial infarction is associated with right ventricular (RV) remodeling. Glypican-6 (GPC6), a member of the membrane proteoglycan family, plays a significant role in cardiac remodeling. This study aims to determine if GPC6 can predict RV remodeling after percutaneous coronary intervention (PCI) in patients with non-ST segment elevation myocardial infarction (NSTEMI).

Methods: The study enrolled 164 consecutive patients with NSTEMI and controls. It compared baseline plasma GPC6 levels, echocardiography, and laboratory parameters between the RV remodeling and non-RV remodeling groups with NSTEMI. Echocardiographic data were measured at baseline and at six months.

Results: GPC6 levels were higher in the NSTEMI group 11.06 ng/mL (4.61-18.17) vs. 5.98 ng/mL (3.81-9.83) compared to the control group in the initial phase. RV remodeling, defined as a ≥ 20% increase in RV end-diastolic area (RV EDA), was observed in 23 patients (30%). After six months, RV EDA increased significantly from baseline 18.68 ± 1.20 cm^2 vs. 24.91 ± 1.08 cm^2, $P < 0.001$. GPC6 was a significant independent predictor of RV remodeling (hazard ratio [HR]: 1.546, 95% confidence interval [CI]: 1.056-2.245, $P < 0.001$). Receiver operating characteristic curve (ROC) analyses showed that GPC6 values > 15.5 ng/mL (area under the curve [AUC] = 0.828, sensitivity: 70%, specificity: 74%, $P < 0.001$) were strong predictors of RV remodeling.

Conclusion: NSTEMI patients should be closely monitored for RV remodeling. GPC6 appears useful in detecting RV remodeling following NSTEMI in patients undergoing PCI.

Keywords: Glypican-6, right ventricular (RV) remodeling, non-ST segment elevation myocardial infarction (NSTEMI), right ventricle

ÖZET

Amaç: Miyokard enfarktüsü sağ ventrikül (RV) yeniden şekillenmesi ile ilişkilidir. Glypican-6 (GPC6) membran proteoglikan ailesinin bir üyesidir ve kardiyak yeniden şekillenmede önemli rol oynar. Çalışmamızın amacı, GPC6'nın ST elevasyonu olmayan miyokard enfarktüsü (NSTEMI) geçiren hastalarda perkütan koroner girişim (PKG) sonrası RV yeniden şekillenmesini öngörüp öngöremeyeceğini belirlemektir.

Yöntemler: Çalışmaya 164 ardışık NSTEMI ve kontrol grubu hastası dahil edilmiştir. Başlangıç plazma GPC6 düzeyleri, ekokardiyografi ve laboratuvar parametreleri NSTEMI'li RV remodelling ve non-RV remodelling gruplar arasında karşılaştırıldı. Ekokardiyografik veriler başlangıçta ve 6. ayda ölçüldü.

Bulgular: GPC6 düzeyleri NSTEMI grubunda [11,06 ng/mL (4,61-18,17) - 5,98 ng/mL (3,81-9,83)] kontrol grubuna kıyasla yüksekti. RV remodelling insidansı (RV diyastol sonu alanında ≥%20 artış [RV EDA]) 23 hastada (%30) gözlendi. RV EDA 6 ay sonra başlangıca göre anlamlı şekilde arttı (18,68 ± 1,20 cm^2 vs. 24,91 ± 1,08 cm^2, $P < 0,001$). GPC6, RV yeniden şekillenmesinin anlamlı bir bağımsız öngörücüsü olmuştur (tehlike oranı: 1.546, %95 güven aralığı: 1,056-2,245, $P < 0,001$). Alıcı işletim karakteristik eğrisi (ROC) analizleri, GPC6 değerlerinin > 15,5 ng/mL (AUC = 0,828, duyarlılık: %70, özgüllük: %74, $P < 0,001$) olmasının RV yeniden şekillenmesinin güçlü öngördürücüsü olduğunu göstermiştir.

Sonuç: NSTEMI hastaları RV yeniden şekillenmesi açısından yakından izlenmelidir. GPC6'nın PKG uygulanan hastalarda NSTEMI'yi takiben RV yeniden şekillenmesini saptamada yararlı olduğu görülmektedir.

Anahtar Kelimeler: Glypican-6, RV yeniden şekillenmesi, NSTEMI, sağ ventrikül

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Received: December 23, 2023
Accepted: March 18, 2024

Cite this article as: Küçük U, Volina E, Arslan K. Can glypican-6 levels be used to determine right ventricular remodeling after non-ST segment elevation myocardial infarction? *Turk Kardiyol Dern Ars.* 2024;52(5):307-314.

DOI:10.5543/tkda.2024.15672

Right ventricular (RV) failure and remodeling can result from various pathological conditions. Pulmonary hypertension, obstructive sleep apnea syndrome, and RV myocardial infarction are among the most common causes of RV failure.[1-3] These conditions alter the myocardial architecture, contractility, and chamber geometry of the RV.[4]

Glypican-6 (GPC6) belongs to the heparan sulfate proteoglycan family. Glypicans (GPC) play a prominent role in cell differentiation, replication, and the signaling pathways of fibroblast growth factors, particularly in remodeling the cardiac extracellular matrix (ECM).[5] GPC is tethered to the extracellular leaflet of the plasma membrane by glycosylphosphatidylinositol (GPI).[6] A recent study has shown that GPC6 may be useful in detecting low left ventricular ejection fraction (LVEF).[7] An animal study has indicated that mice exposed to excessive volume in cases of end-stage heart failure exhibited elevated levels of GPC6.[8] Myocyte damage triggers cardiac remodeling, influenced by ECM, fibroblasts, and inflammatory pathways.[9]

GPC6 appears to be involved in cardiomyocyte remodeling; however, our understanding of this role is limited. Specifically, there is scant information regarding how GPC6 contributes to cardiac remodeling and failure, indicating a gap in our current knowledge. This study aims to investigate the impact of non-ST segment elevation myocardial infarction (NSTEMI) on RV structure and function, as well as the role of GPC6 levels in RV remodeling.

Materials and Methods

Study Population

This case-control, cross-sectional study was conducted in the cardiology unit from August 2022 to March 2023. It comprised two groups: NSTEMI (77 patients) and a control group (87 patients). Coronary angiography (CAG) was performed on all patients. The control group comprised patients randomly selected who underwent CAG due to myocardial ischemia, as demonstrated by a coronary exercise stress test or myocardial perfusion scintigraphy, with no evidence of coronary artery disease (coronary luminal diameter stenosis less than 30%). At the second stage, only NSTEMI patients were evaluated. Baseline and six-month follow-up echocardiographic data were collected. RV remodeling is defined as a 20% increase in RV end-diastolic area (RV EDA).[10] A threshold of 20% increase in RV EDA was used to differentiate patients with and without RV remodeling post-infarction. NSTEMI was diagnosed according to current guidelines.[11]

The exclusion criteria included known coronary artery disease, renal disease (estimated Glomerular Filtration Rate, eGFR < 30 mL/min/1.73 m^2), stroke, coronary artery bypass graft (CABG), prosthetic heart valves, LVEF below 40%, any cardiomyopathy, moderate or severe stenosis or insufficiency of one or more heart valves, active infection and/or malignant disease, pulmonary hypertension, congenital heart disease, LV remodeling (LV remodeling following NSTEMI has been conventionally defined as ≥ 20% increase in LV end-diastolic volume (LVEDV) from baseline), poor echocardiographic window, and patients under the age of 18.

The study approval was obtained from the Ethics Committee of Clinical Research of Çanakkale Onsekiz Mart University (Approval Number: 2022-YÖNP-0066, Date: 2022.07.27). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained before the study.

Echocardiographic Imaging Protocol

Transthoracic echocardiography (TTE) was performed using the Philips EPIQ 7 Cardiac Ultrasound (Bothell, WA, USA). All examinations were conducted according to the guidelines.[12] TTE was performed within 24 hours of admission and at three- and six-month follow-up visits. All imaging data were digitally archived (QLab 11.0, Philips, Andover, MA). TTE examinations were conducted following blood pressure (BP) measurements. The biplane Simpson method was employed to calculate the LVEF. In the RV-focused apical 4-chamber view, the RV endocardial borders were manually traced to measure the RV end-diastolic area (EDA) and end-systolic area (ESA). Right ventricular wall thickness (RVWT) and right ventricular internal diameter (RVID) were assessed to determine RV dimensions. RVWT was obtained from the left parasternal view in the diastole, and the right parasternal long-axis view of the basal cavity was used to measure RVID at the end of diastole. The tricuspid annular plane systolic excursion (TAPSE) was measured by positioning the cursor along the tricuspid lateral annulus. A four-chamber apical view at end-systole was used to trace the right atrial area. Peak tricuspid lateral annular systolic velocity (s'), an indicator of RV systolic function, was measured using an apical 4-chamber window. RV global longitudinal strain (RVGLS) was calculated by manually tracing the RV endocardium in the RV-focused apical four-chamber view, with auto-generated RV longitudinal strain incorporating both the free wall and septum.

Coronary Angiography Evaluation

Coronary angiography (GE Healthcare Innova 2100, New Jersey, USA) was performed by a cardiologist. Several image planes were used to define the lesions causing the infarction. The integration of CAG imaging (identifying coronary arteries with thrombus, ulcerated plaque, lumen dissection, or flaps), electrocardiography, and TTE facilitated the identification of the infarct-related artery (IRA). In some cases, balloon predilatation was performed before coronary stenting, following intravenous heparin administration (70 U/kg bolus) into the IRA. In patients without contraindications, isosorbide dinitrate was administered prior to obtaining the initial angiographic views to rule out coronary slow flow phenomena. Patients without contraindications were administered isosorbide dinitrate, after which imaging was conducted.[13,14]

An Analysis of GPC-6

Blood samples were collected immediately after the percutaneous coronary intervention (PCI). To prevent clotting,

ABBREVIATIONS

CABG	Coronary artery bypass grafting
CAG	Coronary angiography
DES	Drug-eluting stents
GPC6	Glypican-6
NSTEMI	Non-ST segment elevation myocardial infarction
RV EDA	Right ventricular end-diastolic area
STEMI	ST-elevation myocardial infarction
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography

ethylenediaminetetraacetic acid (EDTA) was used as an anticoagulant. After centrifugation, plasma was stored at -80 ^{0}C until assayed. Plasma GPC6 levels were measured using the GPC6 enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory). Blood samples were collected within the first 12 hours post-procedure. There was no statistical difference in the timing of blood draws between patients with and without RV remodeling.

Statistical Analysis

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 19.0 (SPSS Inc., Chicago, IL, USA). The minimum sample size for GPC6 analysis was determined to be 68 individuals to achieve a 90% test power at a 5% alpha level, calculated using G*Power software (version 3.1.9.6). The Kolmogorov-Smirnov tests assessed the normality of continuous variables. Data were expressed as means and standard deviations, or medians and interquartile ranges (IQR). Categorical variables were reported as numbers (n) and percentages (%). Student's t-tests were applied to normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. The Chi-square test or Fisher's Exact test was used to compare probabilities among categorical variables. Depending on data normality, Pearson's and Spearman's correlation analyses were performed. Univariate and multivariate Cox regression analyses identified variables independently associated with RV remodeling. Based on the results of the univariate analysis, we employed the stepwise method to conduct multivariate Cox regression analyses. GPC6 and hsTroponin levels were assessed using receiver operating characteristic curves to determine the optimal predictive values for RV remodeling. Statistical significance was set at $P < 0.05$.

Reproducibility

Twenty patients were randomly selected, and measurements were repeated under identical baseline conditions. The reproducibility of the echocardiographic imaging parameters obtained via TTE was assessed using the coefficient of variation between the measurements, resulting in 4% intra-assay and 2% inter-assay coefficients of variation.

Results

In the initial phase, the NSTEMI and control groups were compared. GPC6 levels were significantly higher in the NSTEMI group (11.06 [4.61-18.17]) compared to the control group (5.98 [3.81-9.83]; $P < 0.001$) (Table 1). Subsequently, 77 NSTEMI patients were categorized into two groups based on the presence or absence of RV remodeling at the end of 6 months. GPC6 levels were lower in the group without RV remodeling (6.22 [3.39-15.58]) than in the group with RV remodeling (18.34 [13.55-32.0], $P < 0.001$) (Table 2).

At six months follow-up, a significant increase in RV EDA was observed in patients with RV remodeling (18.68 ± 1.20 vs. 24.91 ± 1.08 cm^2, $P < 0.001$), while it remained unchanged in patients without RV remodeling (20.00 ± 1.25 vs. 19.61 ± 2.42 cm^2, $P = 0.778$). RV ESA increased significantly in patients with RV remodeling (8.74 ± 1.00 vs. 9.23 ± 1.24 cm^2, $P = 0.045$) and decreased significantly in those without RV remodeling (9.72 ± 1.05 vs. 8.99 ± 1.42 cm^2, $P = 0.018$) (Table 3).

Table 1. Baseline Demographic and Laboratory Parameters of the NSTEMI Group and the Control Group

	NSTEMI (n = 77)	Control (n = 87)	*P*
Age (years)	59.86 ± 10.99	60.09 ± 10.74	0.890
Male, n (%)	51 (66.2)	46 (52.9)	0.082
BMI (kg/m^2)	27.99 ± 4.76	28.14 ± 4.96	0.846
HT, n (%)	19 (24.7)	25 (28.7)	0.558
DM, n (%)	13 (16.9)	8 (9.2)	0.216
Dyslipidemia, n (%)	9 (11.7)	5 (5.7)	0.281
Smokers, n (%)	8 (10.4)	6 (6.9)	0.604
Family History of CAD, n (%)	7 (9.1)	9 (10.3)	0.995
Heart Rate (bpm) LVEF (%)	76.81 ± 15.60 51.5 ± 6.29	73.28 ± 12.63 60.2 ± 2.4	0.117 <0.001
SBP (mmHg)	126.51 ± 16.35	122.77 ± 15.68	0.139
DBP (mmHg)	73.98 ± 9.21	74.18 ± 8.56	0.888
Glucose (mg/dL)	107 (91.5-132)	99 (88.7-117.7)	0.091
Creatinine (mg/dL)	0.99 ± 0.52	0.93 ± 0.66	0.520
LDL (mg/dL)	111.81 ± 37.96	106.83 ± 38.23	0.426
Peak Hs-TnT (ng/L)	60 (24-135.5)	13.15 (11.8-14.1)	<0.001
CRP (mg/L)	2.15 (0.77-8.29)	1.7 (1.2-2.5)	0.167
Glypican-6 (ng/mL)	11.06 (4.61-18.17)	5.98 (3.81-9.83)	<0.001

BMI, Body Mass Index; CAD, Coronary Artery Disease; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; Hs-TnT, High-Sensitivity Cardiac Troponin T; HT, Hypertension; LDL, Low-Density Lipoprotein; LVEF, Left Ventricular Ejection Fraction; NSTEMI, Non-ST Segment Elevation Myocardial Infarction; SBP, Systolic Blood Pressure.

Table 2. Comparison of Patients with Right Ventricular Remodeling Versus Patients Without Right Ventricular Remodeling at Follow-up

	RV Remodeling		
	Without RV Remodeling (n = 54)	**With RV Remodeling (n = 23)**	***P***
Age (years)	59.93 ± 11.51	59.70 ± 9.92	0.930
Male, n (%)	34 (63)	17 (73.9)	0.505
BMI (kg/m^2)	27.30 ± 4.15	29.62 ± 5.73	0.088
HT, n (%)	14 (25.9)	5 (21.7)	0.919
DM, n (%)	10 (18.5)	3 (13)	0.744
Dyslipidemia, n (%)	8 (14.8)	1 (4.3)	0.265
Smokers, n (%)	5 (9.3)	3 (13)	0.689
Family History of CAD, n (%)	3 (5.6)	4 (17.4)	0.187
Heart Rate (bpm)	77.31 ± 15.97	75.61 ± 14.99	0.656
SBP (mmHg)	128.37 ± 14.59	122.13 ± 19.55	0.178
DBP (mmHg)	75.20 ± 9.25	71.13 ± 8.63	0.070
Culprit Vessel			
LMCA/LAD	12 (22.2)	11 (47.8)	0.048
LCx	21 (38.9)	5 (21.7)	0.414
RCA	14 (25.9)	6 (26.1)	0.899
Multivessel Coronary Disease	11 (20.4)	7 (30.4)	0.509
LVEF (%)	50.59 ± 6.92	53.65 ± 3.78	0.050
Post-PCI Medication			
ACEi/ARB	53 (98.1)	22 (95.7)	0.511
Statin	54 (100)	23 (100)	-
Beta-blocker	49 (90.7)	18 (78.3)	0.154
Spironolactone	5 (9.3)	3 (13.0)	0.689
Furosemide	3 (5.6)	4 (17.4)	0.187
Echocardiographic Data			
RVWT, (mm)	5.11 ± 0.65	4.58 ± 0.72	0.004
RVID, (mm)	34.05 ± 2.42	32.82 ± 1.52	0.028
RV EDA (cm^2)	20.00 ± 1.25	18.68 ± 1.20	<0.001
RV ESA (cm^2)	9.72 ± 1.05	8.74 ± 1.00	<0.001
TAPSE (mm)	18.48 ± 0.94	18.82 ± 1.08	0.206
RVGLS (%)	21.76 ± 1.53	19.93 ± 0.93	<0.001
RV s' (cm/s)	12.0 ± 1.41	11.0 ± 1.69	0.442
RA Area (cm^2)	11.30 ± 0.97	9.71 ± 1.52	<0.001
Laboratory Parameters			
Glucose (mg/dL)	107 (25-133)	106 (90.7-132)	0.929
Creatinine (mg/dL)	1.13 ± 0.87	0.93 ± 0.24	0.126
LDL (mg/dL)	112.64 ± 38.43	111.43 ± 38.17	0.903
Peak Hs-TnT (ng/L) NT-proBNP (pg/mL)	53.5 (22.75-123.5) 90 (55.75-234)	128 (45.0-257.0) 339 (68.5-524.2)	0.012 0.007
CRP (mg/L)	1.80 (0.25-7.15)	2.20 (1.72-11.40)	0.028
Glypican-6 (ng/mL)	6.22 (3.39-15.58)	18.34 (13.55-32.0)	<0.001

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; BMI, Body Mass Index; CAD, Coronary Artery Disease; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; Hs-TnT, High-Sensitivity Cardiac Troponin T; HT, Hypertension; LAD, Left Anterior Descending Coronary Artery; LCx, Left Circumflex Artery; LDL, Low-Density Lipoprotein; LMCA, Left Main Coronary Artery; LVEF, Left Ventricular Ejection Fraction; NSTEMI, Non-ST Segment Elevation Myocardial Infarction; NT-proBNP, N-terminal Pro-Brain Natriuretic Peptide; RA, Right Atrium; RCA, Right Coronary Artery; RV, Right Ventricle; RV EDA, Right Ventricular End-Diastolic Area; RV ESA, Right Ventricular End-Systolic Area; RVGLS, Right Ventricular Global Longitudinal Strain; RVID, Right Ventricular Internal Diameter; RVWT, Right Ventricular Wall Thickness; s', Pulsed-Wave Doppler Tissue Imaging-Derived Peak Systolic Myocardial Velocity; SBP, Systolic Blood Pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion.

Table 3. Echocardiographic Parameters of Right Ventricular Remodeling

	RV Remodeling					
	With RV Remodeling			Without RV Remodeling		
Echocardiographic Data	**Baseline**	**6 Months**	***P***	**Baseline**	**6 Months**	***P***
RV EDA (cm^2)	18.68 ± 1.20	24.91 ± 1.08	<0.001	20.00 ± 1.25	19.61 ± 2.42	0.778
RV ESA (cm^2)	8.74 ± 1.00	9.23 ± 1.24	0.045	9.72 ± 1.05	8.99 ± 1.42	0.018
TAPSE (mm)	18.82 ± 1.08	19.21 ± 1.12	0.109	18.48 ± 0.94	18.56 ± 1.01	0.068
RA Area (cm^2)	9.71 ± 1.52	12.24 ± 2.06	0.001	11.30 ± 0.97	11.02 ± 1.53	0.533
RVWT, (mm)	4.58 ± 0.72	4.43 ± 0.77	0.157	5.11 ± 0.65	4.93 ± 0.91	0.062
RVID, (mm)	32.82 ± 1.52	34.05 ± 2.42	0.074	34.05 ± 2.42	33.88 ± 2.53	0.083
RVGLS (%)	19.93 ± 0.93	18.65 ± 2.10	0.027	21.76 ± 1.53	21.96 ± 1.56	0.109
RV s' (cm/s)	11.0 ± 1.69	10.43 ± 1.30	0.068	12.0 ± 1.41	11.85 ± 2.75	0.667

RA, Right Atrium; RV, Right Ventricle; RV EDA, Right Ventricular End-Diastolic Area; RV ESA, Right Ventricular End-Systolic Area; RVGLS, Right Ventricular Global Longitudinal Strain; RVID, Diastolic Right Ventricular Internal Diameter; RVWT, Right Ventricular Wall Thickness; s', Pulsed-Wave Doppler Tissue Imaging-Derived Peak Systolic Myocardial Velocity; TAPSE, Tricuspid Annular Plane Systolic Excursion.

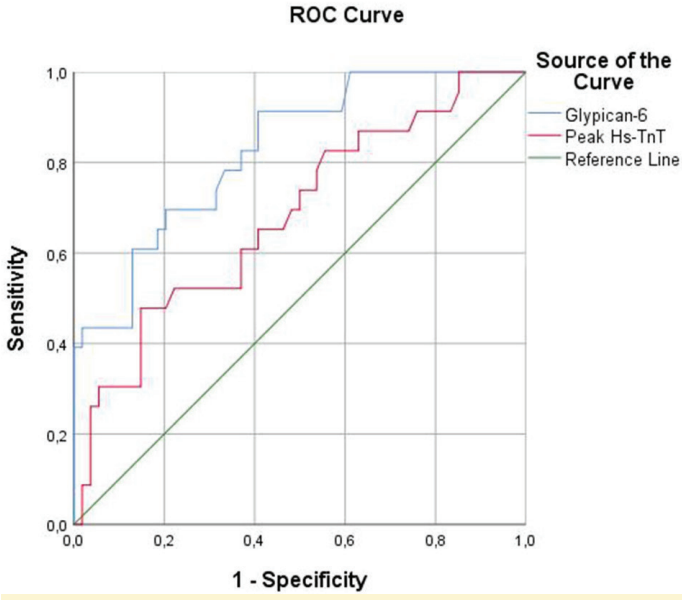

Figure 1. Receiver operating characteristic (ROC) analyses for Glypican-6 for predicting right ventricular (RV) remodeling in non-ST elevation myocardial infarction (NSTEMI) patients.

GPC6 showed significant correlations with C-reactive protein (CRP) (P < 0.001, r = 0.412), peak high-sensitivity troponin T (Hs-TnT) (P < 0.001, r = 0.329), N-terminal pro-brain natriuretic peptide (NT-proBNP) (P < 0.001, r = 0.487), change in RV EDA (P < 0.001, r = 0.627), change in RV ESA (P = 0.032, r = 0.306), and change in RVGLS (P = 0.014, r = -0.420).

Receiver operating characteristic (ROC) analysis indicated that GPC6 is statistically significant in patients with RV remodeling. The optimal cutoff value for predicting RV remodeling was identified as 15.5 ng/mL for serum GPC6. At this level, serum GPC6 demonstrated a sensitivity of 70% and a specificity of 74% in predicting the development of RV remodeling. The mean area under the ROC curve for serum GPC6 was 0.828 (range 0.732-0.924, P < 0.001). In comparison, serum peak Hs-TnT at 71 ng/L exhibited a sensitivity of 55% and a specificity of 34% for predicting RV remodeling. As a predictor of patients with RV remodeling, serum peak Hs-TnT had a mean area under the ROC curve of 0.702 (range, 0.571-0.833, P = 0.008) (Figure 1).

A univariate and multivariate Cox regression analysis was performed to evaluate the factors affecting RV remodeling. Variables analyzed in the univariate analysis included age, gender, body mass index (BMI), diabetes mellitus (DM), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension (HT), smoking status, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), spironolactone, furosemide, peak Hs-TnT, CRP, multivessel coronary disease, and the left main coronary artery/left anterior descending artery (LMCA/LAD) as the culprit vessel. GPC6, peak Hs-TnT, and multivessel coronary disease were identified as significant independent predictors of RV remodeling with hazard ratios (HR) of 1.546 (P < 0.001), 1.002 (P = 0.034), and 1.109, (P = 0.028), respectively (Table 4).

Discussion

In our study, GPC6 levels were significantly higher in groups compared to those without remodeling. GPC6, peak Hs-TnT, and multivessel coronary disease emerged as significant independent predictors of RV remodeling.

RV failure is considered a significant risk marker following acute myocardial infarction (AMI).[15] While the focus in AMI typically centers on the LV, the RV can also be affected and contribute to overall prognosis and outcomes, such as LV dysfunction, arrhythmias, cardiogenic shock, and cardiac death.[16] A recent study revealed that deteriorating RV function, particularly a reduction in RV ejection fraction, significantly correlated with increased mortality risk within the first month among AMI patients presenting with shock. These findings underscore the critical role of RV function in AMI patients experiencing shock, highlighting its potential as a prognostic indicator for mortality risk assessment.[17] However, the importance of RV in NSTEMI has been poorly defined.

Table 4. Univariate and Multivariate Cox Regression Analysis to Identify Markers of Right Ventricular Remodeling

	Univariate			Multivariate		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	0.998	0.955-1.044	0.933			
Gender	1.667	0.565-4.919	0.355			
BMI	1.110	0.996-1.236	0.069			
DM	1.515	0.376-6.109	0.559			
HT						
SBP	0.981	0.948-1.016	0.282			
DBP	0.960	0.906-1.018	0.170			
Smoker	0.680	0.148-3.119	0.620			
Spironolactone	2.027	0.714-5.760	0.039	1.078	0.510-7.669	0.148
Furosemide	3.579	0.732-17.497	0.115			
ACEi/ARB	0.415	0.025-6.936	0.541			
Peak Hs-TnT	1.004	1.001-1.008	0.022	1.002	0.997-1.007	0.034
CRP	1.075	0.985-1.172	0.040	1.089	0.977-1.214	0.124
LMCA/LAD Culprit Vessel	1.271	1.099-1.751	0.042	1.025	1.050-1.678	0.071
Multivessel Coronary Disease	1.432	1.078-3.412	0.034	1.109	1.092-2.103	0.028
Glypican-6	1.646	1.067-2.230	0.002	1.546	1.056-2.245	<0.001

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; BMI, Body Mass Index; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; Hs-TnT, High-Sensitivity Cardiac Troponin T; HT, Hypertension; LAD, Left Anterior Descending Coronary Artery; LMCA, Left Main Coronary Artery; SBP, Systolic Blood Pressure.

Most patients receiving emergent revascularization retained RV function.[18] Patients with acute anterior myocardial infarctions (MIs) exhibited significantly increased RV volumes post-MI, whereas those with inferior MIs did not.[19] These findings suggest that RV remodeling is more likely to occur after an MI when an anterior infarct is present. Similarly, in our study, an LMCA/LAD lesion was more frequently found in the group with RV remodeling. However, the expected RV remodeling in the right coronary artery (RCA) was not significant, likely due to differences in pathogenesis between patients diagnosed with NSTEMI and ST-elevation myocardial infarction (STEMI).

In a study evaluating RV function in 147 AMI patients using cardiac magnetic resonance imaging, 17% were found to have RV dysfunction.[20] Additionally, another study assessing RV myocardial infarction using radionuclide angiography found permanent RV dysfunction in approximately one-third of patients within three months after infarction.[21] In our study, a statistical change was observed in RVGLS, which could be used to compare RV systolic function between the groups at the end of study. These results may be influenced by the definition of RV dysfunction, patient diagnoses, follow-up periods, and the techniques used to examine RV functions.

Cardiac remodeling involves alterations in the heart's cellular and extracellular matrix, such as cardiomyocyte hypertrophy, apoptosis, and fibrosis.[22] While glypicans play significant roles in cardiovascular biology, their direct relationship with RV dysfunction or their specific involvement in the pathophysiology of RV remodeling is not well-established or extensively studied. The effects of GPC6 on the cardiovascular system are not well understood. Research has shown that GPC6 regulates cardiomyocyte growth in clinical and experimental heart failure.[8] In another study, its utility in predicting post-MI LV dysfunction has been demonstrated.[7] The clinical significance of GPC6's effects on RV EDA is also notable. RV EDA expansion may indicate a poor prognosis in cardiovascular disease and increase the risk of heart failure. A recent study found that post-RV infarction remodeling was associated with mortality and heart failure (HF) hospitalization, independent of RV systolic function.[23] In our study, GPC6 levels were higher in patients with RV remodeling, and GPC6 was a significant independent predictor of RV remodeling in NSTEMI patients. Therefore, it is conceivable that GPC6 may modulate cardiovascular risk factors by affecting RV EDA. Clinical monitoring of GPC6 levels may be useful in assessing patients' prognosis and determining treatment plans.

CRP levels were measured and found to be higher in the RV remodeling group. We also found a significant correlation between CRP and GPC6. Furthermore, GPC6 levels, similar to those of inflammatory markers, were increased in the RV remodeling group. This suggests that GPC6 mediates inflammation in the acute phase. This theory is supported by the fact that both GPC6 and CRP levels were higher among NSTEMI patients compared to the healthy group.

Increased levels of NT-proBNP, associated with RV remodeling, may reflect the development and progression of HF.[24] It is important to use NT-proBNP in assessing RV function and determining RV remodeling. In our study, a correlation was observed between NT-proBNP and GPC6 levels, suggesting

that both NT-proBNP and GPC6 play an important role in RV remodeling and may be indirectly related to each other.

The association of GPC6 with RV remodeling holds clinical application potential. Using GPC6 expression as a marker for RV remodeling may enable early diagnosis of RV dysfunction and intervention to prevent the progression of cardiovascular diseases. Additionally, clinical trials are needed to assess whether pharmacological or genetic interventions targeting GPC6 are effective in treating or preventing RV remodeling.

Our study is a single-center study, and GPC6 levels were measured at the time of diagnosis. RV remodeling is a complex process affected by several factors. While analyzing serum GPC6 levels six months post-event may offer insights into GPC6's long-term impact on RV remodeling, the relevance of this delayed measurement in relation to RV remodeling remains uncertain. Considering the timing of serum GPC6 analysis and its possible correlation with RV remodeling, it was decided to measure serum GPC6 levels within the first 12 hours after hospital admission. This approach aims to detect early changes and immediate responses following an NSTEMI. It is important to note that the focus of the current study was on acute-phase measurements to delineate early associations and responses to NSTEMI. While cardiac magnetic resonance imaging and 3D echo modeling are important for evaluating complex cardiac structures like RV, these were not performed due to high costs and extensive time requirements. Despite its limitations, we believe our study is the first of its kind in the literature, providing crucial insights into a condition that is frequently undiagnosed in clinical settings. Although no mortality was observed among our study participants during the six-month follow-up, we lack data on long-term outcomes. We anticipate that future multicenter, long-term follow-up studies will address these gaps. The kit used in the study is reasonably priced; however, this paper does not include the cost of the review or cost-effectiveness analyses.

Conclusion

In conclusion, this study highlights the role of GPC6 in RV remodeling and opens up new avenues for research and clinical applications in cardiovascular health. A deeper understanding of the relationship between GPC6 and RV remodeling could lead to significant advancements in the prevention and treatment of cardiovascular diseases. GPC6 has potential as a predictive marker for RV remodeling in patients with NSTEMI, offering insight into which patients may require regular echocardiographic monitoring post-NSTEMI.

Ethics Committee Approval: The study approval was obtained from the Ethics Committee of Clinical Research of Çanakkale Onsekiz Mart University (Approval Number: 2022-YÖNP-0066, Date: 2022.07.27).

Informed Consent: Informed consent was obtained before the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – U.K., E.V., K.A.; Design – U.K., E.V., K.A.; Supervision – U.K., E.V., K.A.; Resource – U.K., E.V., K.A.; Materials – U.K., E.V., K.A.; Data Collection and/or Processing - U.K., E.V., K.A.; Analysis and/or Interpretation - U.K., E.V., K.A.; Literature Review – U.K., E.V., K.A.; Writing – U.K., E.V., K.A.; Critical Review – U.K., E.V., K.A.

Use of AI for Writing Assistance: The authors declare that AI-assisted technologies were not used in this study.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: This study was supported by Çanakkale Onsekiz Mart University The Scientific Research Coordination Unit (Project number: THD-2022-4174).

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