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Myocardial Mechanical Dispersion Predicts Adverse Cardiac Remodeling in Patients with ST Segment Elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention

Miyokardiyal Mekanik Dispersiyon, Primer Perkütan Koroner Girişim Uygulanan ST Yükselmeli Miyokart Enfarktüslü Hastalarda Olumsuz Kardiyak Yeniden Şekillenmeyi Öngörür

ABSTRACT

Objective: The aim of the study was to investigate whether increased left ventricular mechanical dispersion is an early predictor for adverse cardiac remodeling in ST-segment elevation myocardial infarction patients who had post-percutaneous coronary intervention thrombolysis in myocardial infarction (TIMI) flow grade > 2.

Methods: A total of 119 post-percutaneous coronary intervention ST elevation myocardial infarction patients with TIMI flow grade >2 were prospectively included in the study. Left ventricular global longitudinal strain was quantified by 2-dimensional speckletracking echocardiography, and left ventricular mechanical dispersion was determined at baseline and after 1 year to assess adverse cardiac remodeling. The levels of circulating biomarkers were measured at the baseline. TIMI score and the Global Registry of Acute Coronary Events score systems were used to evaluate the prognosis of patients.

Results: Patients with high quartile versus low quartile of left ventricular mechanical dispersion exerted higher Global Registry of Acute Coronary Events and TIMI score grades, left ventricular end-systolic volume, global longitudinal strain, and levels of the N-terminal fragment of brain natriuretic peptide and lower left ventricular ejection fraction. Multivariate log regression showed that N-terminal fragment of brain natriuretic peptide > 953 pg/mL, global longitudinal strain > –8%, and high quartile of left ventricular mechanical dispersion remained independent predictors for adverse cardiac remodeling. Addition of left ventricular mechanical dispersion to the N-terminal fragment of brain natriuretic peptide improved the discriminative potency of the whole model.

Conclusion: Measurement of left ventricular mechanical dispersion might be useful in determining the risk of adverse cardiac remodeling in post-percutaneous coronary intervention ST elevation myocardial infarction patients.

Keywords: Myocardial revascularization, percutaneous coronary intervention, acute coronary syndrome, cardiac function, heart failure

ÖZET

Amaç: Bu çalışmanın amacı perkütan koroner girişim yapılmış, işlem sonrası TIMI (Thrombolysis in Myocardial Infarction) akımı >2 olan ST yükselmeli miyokart infarktüsü hastalarında artmış sol ventrikül mekanik dispersiyonunun (SVMD) sol ventrikül olumsuz yeniden şekillenmesinin erken belirleyicisi olup olmadığını araştırmaktı.

Yöntem: Çalışmaya TIMI akım hızı >2 olan perkütan koroner girişim yapılmış toplam 119 ST yükselmeli miyokart infarktüsü hastası prospektif olarak dahil edildi. İki boyutlu benek takibi ekokardiyografi yöntemiyle sol ventrikül global uzunlamasına *strain* (GLS) belirlendi. Sol ventrikül olumsuz yeniden şekillenmesini belirlemek için başlangıçta ve işlemden 1 yıl sonra SVMD belirlendi. Biyobelirteç seviyeleri başlangıçta ölçüldü. Hastaların prognozunu belirlemek için TIMI ve GRACE skorları kullanıldı.

Bulgular: LVMD'nin düşük çeyreğindeki hastalara kıyasla, yüksek çeyrekteki hastalar daha yüksek GRACE ve TIMI skoru, sol ventrikül sistol sonu hacimi, GLS, N-terminal beyin natriüretik peptid (BNP) ve daha düşük sol ventrikül ejeksiyon fraksiyonuna sahipti. Çok değişkenli log regresyon analizine göre N-terminal BNP'nin >953 pg/ml olması, GLS'nin >%-8 olması ve

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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SVMD'nin yüksek çeyreği, olumsuz yeniden şekillenme için bağımsız öngördürücüler idi. SVMD'nin N-terminal BNP'ye eklenmesi, tüm modelin ayırt edici özelliğini iyileştirdi.

Sonuç: Sol ventrikül mekanik dispersiyonunun ölçümü, perkütan koroner girişim sonrası ST yükselmeli miyokart infarktüsü hastalarında olumsuz yeniden şekillenme riskini belirlemede yardımcı olabilir.

Anahtar Kelimeler: Miyokardiyal revaskülarizasyon, perkütan koroner girişim, akut koroner sendrom, kardiyak fonksiyon, kalp yetmezliği

The management of ST elevation myocardial infarction (STEMI) has considerably evolved over the past 2 decades.[1,2] A broad implementation of the modern strategy of reperfusion, optimal guided-based therapy, has improved clinical outcomes after interventional procedures.[3-5] In connection with these, the in-hospital STEMI mortality rate has dramatically decreased from 17% in the era before reperfusion to 4%-6% currently in percutaneous coronary intervention (PCI) centers, and now it is on the plateau.[6,7] In fact, these causes of CV death result of adverse cardiac remodeling (ACR) due to suboptimal reperfusion due to microvascular obstruction and inflammation, co-existing >50% narrowing of culprit coronary arteries/ ischemic stenotic lesions, comorbidities [type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD)], altered coronary collateral circulation, total chronic coronary occlusion, and also a delay in PCI performing.[7-9] Thus, STEMI remains a challenging clinical condition with a high risk of mortality even after successful PCI.[10]

There is a large body of scientific proof regarding the fact that ACR which is defined as post-STEMI increase in left ventricular (LV) dimension >10% and/or decrease in LV ejection fraction >10% from the baseline is regarded to be a powerful predictor of new-onset heart failure (HF), sudden cardiac death, and poor survival.[11-13] Left ventricular mechanical dispersion (LVMD) reflecting myocardial fiber disarray is determined by speckle-tracking echocardiography and is a strong predictor of ACR.[14] To note, LVMD determined impaired LV systolic function despite normal LV size.[14] Left ventricular mechanical dispersion is strongly associated with regional LV heterogeneity, LV end-systolic volume (LV ESV) index, infarct size, and major atherosclerotic events (MACEs).[15] Yet, LVMD was found to be associated with newly HF and ventricular arrhythmias.[16] Moreover, LVMD more than other strain parameters predicted MACEs and poor prognosis of HF.[17] Although LVMD has been previously determined to be a powerful indicator of ACR having discriminative potency for MACEs, whether this parameter predicts ACR in STEMI patients with complete PCI remains to be uncertain and is under scientific discussion. We hypothesized that increased LVMD predicts ACR in post-STEMI patients who had post-PCI thrombolysis in myocardial infarction (TIMI) flow grade > 2.

Materials and Methods

Study Population

A total of 246 patients with STEMI were prospectively screened according to inclusion criteria (acute STEMI, age > 18 years old, and a lack of contraindications to primary PCI). The patients were urgently admitted to the intensive care unit of "L.T.Malaya TNI NAMSU" during the period between December 2017 and February 2021. Those who were transferred into the intensive care unit during the coronavirus disease-19 (COVID-19) pandemic had demonstrated twice-negative COVID-19 tests (antigen test and polymerase chain reaction test) before hospitalization. We diagnosed acute STEMI according to the 2017 European Society of Cardiology (ESC) guidelines.[18] Using the following exclusion criteria [poor acoustic windows, previous acute myocardial infarction, irregular heart rhythm, atrial fibrillation/flutter, HF with reduced ejection fraction (HFrEF), known malignancy, severe comorbidities (anemia, chronic obstructive lung disease, bronchial asthma, liver cirrhosis, CKD with estimated glomerular filtration rate ≤60 mL/min/1.73 m^2, valvular heart disease, severe secondary valve regurgitation, and active bleeding), and inability to understand and sign the written informed consent], we finally enrolled 134 STEMI patients (Figure 1). Among them, 7 patients had post-STEMI PCI TIMI flow grade ≤2, 5 patients did not give their written informed consent to participate in the study, and 3 patients did not have biochemical monitoring. Thus, study population consisted of 119 STEMI individuals.

Ethical Declaration

The study was approved by the L.T. Malaya National Therapy Institute of the National Academy of Medical Sciences of Ukraine committee for medical research ethics (protocol no. 6; date: May 30, 2017). All procedures were performed according to the 1964 Helsinki Declaration and its later amendments. Written inform consent was given by all participants.

Primary Percutaneous Coronary Intervention

All enrolled patients were treated by primary PCI using the digital x-ray system "Integris Allura" (Philips Healthcare, Best, The Netherlands) and managed by radial (n=187) or femoral (n=59) vascular access. We infused "Ultravist-370" (Bayer Pharma GmbH, Leverkusen, Germany) contrast. Bare-metal stent Rebel™ (Platinum Chromium Coronary Stent System, Boston Scientific, Natick, MA, USA) for primary PCI with implantation in infarct-related artery was performed. All enrolled patients received standard adjuvant treatment.[18]

Determination of ST Elevation Myocardial Infarction Prognosis

We utilized the TIMI score[19] and the Global Registry of Acute Coronary Events (GRACE) score[20] to evaluate a prognosis in post-PCI STEMI patients.

Transthoracic Echocardiography

Left ventricular ejection fraction (LVEF) was calculated by Simpson biplane method, and a senior cardiac ultrasound physician analyzed the images with "Aplio 500" (TUS-A500) Toshiba Medical Systems Corporation (Tokyo, Japan). Data acquisition was performed with 3.5 MHz probe. Left ventricular end-diastolic volume (LV EDV), LV ESV, left atrium volume (LAV) were measured. [21] The LAV index (iLAV) was calculated as a ratio of LAV to the body surface area. Left ventricular global longitudinal

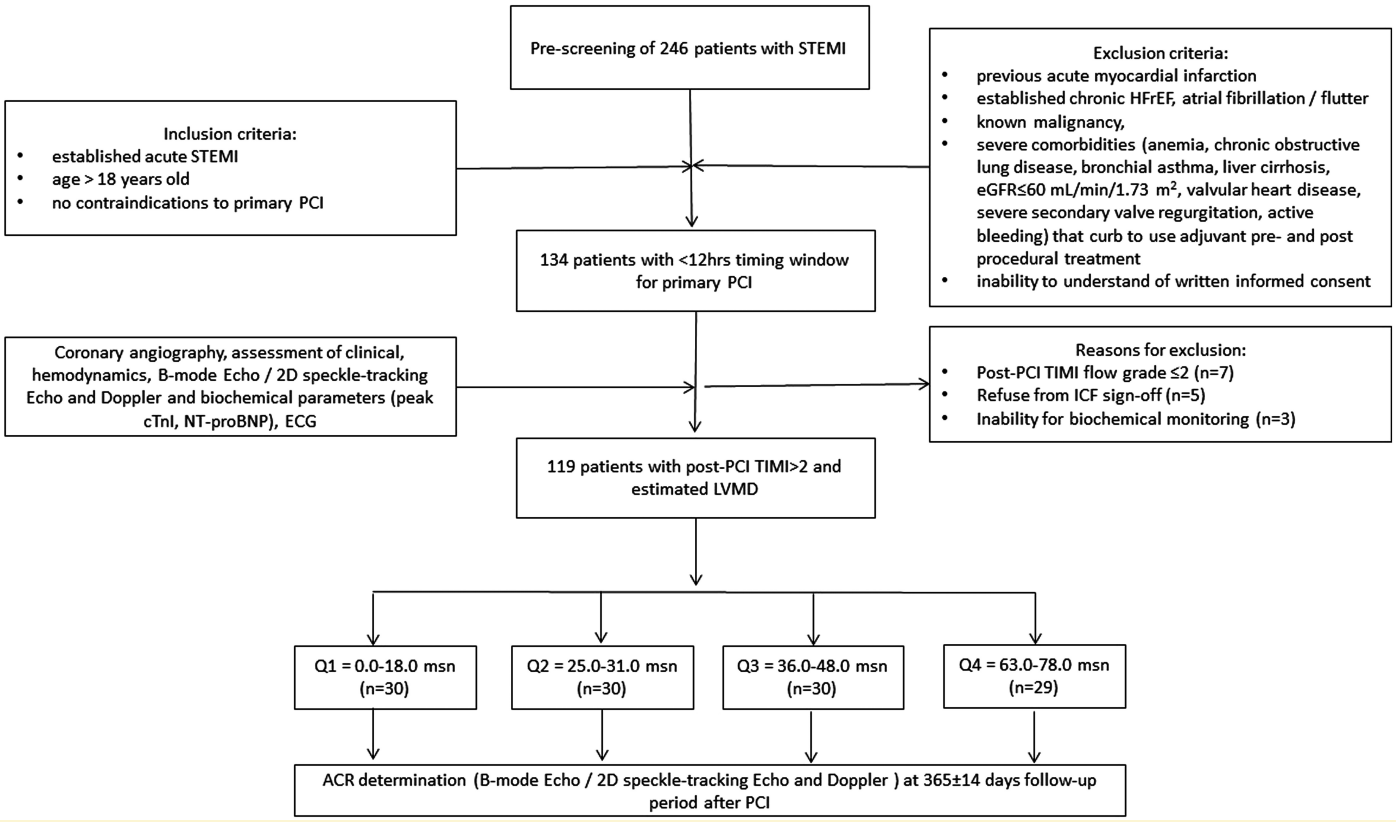

Figure 1. The design of the study: flowchart. cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVMD, left ventricular mechanical dispersion; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; Q, quartile; STEMI, ST segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

strain (GLS) was quantified by two-dimensional (2D) speckle-tracking echocardiography on the apical 4-chamber, 2-chamber, and long-axis views.[22]

Determination of Left Ventricular Mechanical Dispersion

We used speckle-tracking echocardiography in order to measure GLS as the average peak longitudinal strain (PLS) using off-line software (Toshiba Medical Systems Corporation). Longitudinal LVMD was detected as the SD of time from PLS of each segment from 18-segment LV model.[23] For evaluations were assessed from basal and mid-levels in apical 4-chamber, 2-chamber, and long-axis views.

Adverse Cardiac Remodeling Determination

Late ACR was determined as an increase in LV EDV > 10% and/or LV ESV > 10% at 365-day (with the time window ±14 days) follow-up period after PCI.

Concomitant Diseases and Conditions

The status of previous heart disease was evaluated by reviewing source documents (medical records and discharge reports), telephone calls to doctors, and pooling information during contact with the patients. Dyslipidemia was established as an increase in levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides and/or decrease in high-density lipoprotein (HDL) and/or lipid-lowering drug treatment.[24] Hypertension diagnosed in accordance with ESC guidelines as an increase in systolic and/or diastolic blood pressures (BPs)>140/90 mm Hg, respectively, and/or a presence of current treatment with antihypertensive drugs [25] Type 2 diabetes mellitus was determined according to the 2019 American Diabetes Association statement[26] or treatment with antidiabetic agent . Heart failure was diagnosed according to the current 2021 ESC guidelines and defined as symptoms and/or signs of congestion due to an altered structure and/or cardiac dysfunction in association with elevated N-terminal fragment of brain natriuretic peptide (NT-proBNP) levels.[27]

Estimated glomerular filtration rate (eGFR) was estimated using the CKD epidemiology collaboration equation.[28]

Blood Samples

Blood samples were drawn before PCI. After centrifugation, the serum was isolated and stored in plastic tubes until being shipped to the laboratory of immune-chemical and molecular-genetic researches of "L.T.Malaya TNI NAMSU." The troponin I (Tn I) level was detected with chemoluminescent immunoassay (Humalyser 2000, Mannheim, Germany). The average of TnI level was 0.5-50 ng/mL. The NT-proBNP level was measured by commercially available standard kit (R&D Systems GmbH, Wiesbaden-Nordenstadt, Germany). The average of NT-proBNP level was 10-12 000 pg/mL. Creatinine, triglyceride, total cholesterol (enzymatic method), HDL-C (direct assay), and LDL-C (direct assay) were all tested using the "HumaStar 200" Automatic Biochemical Analyzer (HUMAN GmbH, Wiesbaden, Germany) and appropriate commercial reagents.

Statistical Analysis

Statistical analysis was performed using version 21 IBM Statistical Package for Social Sciences Statistics for Windows (IBM Corp., Armonk, NY, USA). The distribution pattern of the variables was analyzed using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± SD when normally distributed. Data that did not follow a normal distribution were represented as the interval between the median and interquartile range. Categorical variables are presented as frequencies (n) and percentages (%). The Mann–Whitney *U*-test was used to compare nonparametric continuous variables. Categorical variables were compared using the χ^2 test, the results of which were presented as percentages. Variables between quartiles were compared using analysis of variance (ANOVA) with the Tukey's test.

To calculate the sample size, we used the following formula:

$$n = \left(\frac{Z_{1-\alpha/2} \times \sqrt{p \times (1-p)}}{\delta} \right)^2$$

$Z_{1-\alpha/2}$ is 1.96, δ represents allowable error which is equal to 0.05, and p represents sensitivity or specificity, which were determined as 0.76 and 0.83 in the previous study of LVMD in predicting adverse outcomes in STEMI. Thus, we found that 118 patients were needed to obtained concise results in this study.

Spearmen's rank correlation was used to measure the strength and direction of association between LVMD and other parameters, such as STEMI risk scores, serum biomarkers, and hemodynamic performances. Univariate and multivariate log regressions with stepwise forward selection process were consequently performed to test the association between variables and ACR. We calculated beta coefficient, SD, odds ratio (OR), and 95% CI for each factor. Receiver operating characteristic (ROC) curves with separate analysis of Youden index were constructed to assess the reliability of the predictive models. The DeLong's test was applied for comparison of area under curve of different models. Predictors of ACR were confirmed using integrated discrimination indices and net-reclassification improvement. The intraclass correlation coefficient was used to determine both inter- and intraobserver reproducibility for LVMD obtained from 40 randomly selected patients. All differences were considered statistically significant ($P < 0.05$).

Results

The patients enrolled in the study were mainly male (88.2%) with a mean age of 59 years who had several cardiovascular comorbidities and risk factors including hypertension (75.6%), T2DM (25.2%), smoking (68.1%), and overweight/obesity determined by body mass index (BMI) >30 kg/m^2 (26.9%) (Table 1).

Almost 52% of STEMI patients have been determined to have anterior acute MI, and 32.8% and 39.5% of all STEMI individuals had single- and multiple-vessel, respectively. Culprit lesions of right coronary artery and left anterior descending artery were found in 38.7% and 47.9% of STEMI patients, respectively. The patients corresponded to the intermediate risk of an unfavorable outcome according to both the GRACE and TIMI risk scores. All STEMI patients were treated with dual antiplatelet therapy and statins, and the majority of them received antagonists of the renin–angiotensin system, mineralocorticoid receptor antagonists, and beta-blockers on their hemodynamic condition at the study entry. The criteria of ACR were met in 49.6% of post-PCI STEMI patients. Figure 2 illustrates examples of measuring GLS in patients with and without LVMD.

The average value of LVMD in the entire STEMI patient group was 36.76 ms (95% CI=22.0 ms-51.0 ms). We divided the entire group of STEMI patients into 4 cohorts depending on quartiles of LVMD. The ranges of LVMD in each quartile are represented in Figure 3. The ranges for Q1, Q2, Q3, and Q4 were 0-18 ms, 25-31 ms, 36-48 ms, and 63-78 ms, respectively.

There were no significant differences among cohorts in demographic and anthropometric parameters (BMI), CV risk factors (hypertension and smoking),number of coronary arteries, systolic and diastolic BPs, heart rate, LV EDV, iLAV, eGFR, biochemical biomarker levels and concomitant medications (Table 1). However, patients with the highest quartile of LVMD frequently had anterior localization of acute MI and exerted significantly higher GRACE and TIMI score grades, LV ESV, GLS, and levels of NT-proBNP and lower LVEF when compared with those who had low quartiles of LVMD. Finally, post-PCI STEMI patients with low quartiles of LVMD had of less ACR than those who had high quartiles ($P=0.039$ for all cases).

Spearmen Correlation Between Left Ventricular Mechanical Dispersion and ST Elevation Myocardial Infarction Risk Scores, Serum Biomarkers, and Hemodynamic Performances

There were positive correlations between LVMD and NT-proBNP ($r=0.44$; $P=0.001$), GRACE score ($r=0.31$; $P=0.001$), TIMI score ($r=0.31$; $P=0.002$), T2DM ($r=0.30$; $P=0.042$), serum levels of LDL-C ($r=0.26$; $P=0.014$), peak Tn I ($r=0.28$; $P=0.016$), eGFR ($r=0.23$; $P=0.012$), early diastolic blood filling to tissue Doppler early diastolic velocity ratio [E/e'] [E/e′] ($r=0.21$; $P=0.048$), and LV ESV ($r=0.33$; $P=0.002$) and negative correlations with GLS ($r=-0.51$; $P=0.001$) and LVEF ($r=-0.38$; $P=0.001$). There were no significant associations of LVMD with age, gender, BMI, number of CV risk factors, number of culprit coronary arteries, systolic and diastolic BP, and concomitant medications. Global longitudinal strain correlated positively with circulating levels of cardiac TnI ($r=0.32$; $P=0.001$) and NT-proBNP ($r=0.380$; $P=0.001$).

Univariate and Multivariate Log Regression Analysis

The univariate stepwise log regression analysis has revealed that GRACE score, NT-proBNP level, peak TnI, LVEF, GLS, and LVMD were found to be predictors for ACR (Table 2). Other variables had P>0.1 and thereby, they were not included into multivariate regressive analysis. Multivariate log regression showed that NT-proBNP, LVEF, GLS, and LVMD remained independent predictors for ACR (Table 2).

Receiver Operating Curve analyses

Receiver operating curve analyses showed that NT-proBNP, GLS > –8%, and high quartile of LVMD were reliable models for ACR (Figure 4). Sensitivity and specificity of the models were 80.8% and 87.5% for LVMD (cutoff point=68 ms), 78.2% and 73.5% for serum NT-proBNP levels (cutoff point=953 pmol/mL), and 82.0% and 66.7% for GLS (cutoff point=–8%), respectively.

Table 1. Characteristics of the Study Population Depending on Quartiles of LVMD

Variables	Entire Group (n=119)	First Quartile (0-18 ms) (n=30)	Second Quartile (25-31 ms) (n=30)	Third Quartile (36-48 ms) (n=30)	Fourth Quartile (63-78 ms) (n=29)	*P*
Demographics and anthropometric parameters						
Age, years [median (IQR)]	59 (50-69)	59 (49-68)	57 (47-58)	61 (53-69)	59 (50-69)	0.177
Male, n (%)	105 (88.2)	29 (96.7)	26 (86.7)	26 (86.7)	24 (82.8)	0.090
Hypertension, n (%)	90 (75.6)	23 (76.7)	23 (76.7)	23 (76.7)	21 (72.4)	0.620
T2DM, n (%)	3 0 (25.2)	7 (23.3)	6 (20.0)	8 (26.7)	9 (31.0)	0.355
Smoking, n (%)	81 (68.1)	24 (80.0)	19 (63.3)	18 (60.0)	20 (69.0)	0.159
BMI > 30 kg/m^2, n (%)	32 (26.9)	8 (6.7)	6 (20.0)	9 (30.0)	9 (31.0)	0.551
Localization of myocardial infarction						
Anterior, n (%)	62 (52.1)	11 (36.7)	20 (66.7)	15 (50.0)	16 (55.2)	0.020
Posterior, n (%)	57 (47.9)	19 (63.3)	10 (33.3)	15 (50.0)	13 (44.8)	0.366
Number of stenotic coronary arteries						
One vessel, n (%)	39 (32.8)	16 (53.3)	8 (26.7)	8 (26.7)	7 (24.1)	0.065
Two vessels, n (%)	47 (39.5)	8 (26.7)	13 (43.3)	12 (40.0)	14 (48.3)	0.279
Three vessels/multiple vessel, n (%)	33 (27.7)	6 (20.0)	9 (30.0)	10 (33.3)	8 (27.6)	0.381
Culprit coronary arteries						
Left main coronary artery, n (%)	5 (4.2)	1 (5.0)	1 (5.0)	1 (5.0)	2 (10.5)	0.492
LAD, n (%)	57 (47.9)	11 (36.7)	17 (56.7)	14 (46.7)	15 (51.7)	0.121
RCA, n (%)	46 (38.7)	13 (43.3)	10 (33.3)	12 (40.0)	11 (37.9)	0.426
Circumflex artery, n (%)	9 (7.6)	5 (3.3)	0	2 (6.7)	2 (6.9)	0.026
Stratification of STEMI at risk						
GRACE risk score (grades)	140 ± 35	134 ± 25	146 ± 27	149 ± 19	153 ± 16	0.047
TIMI risk score (grades)	4.1 ± 2.6	3.4 ± 1.9	3.7 ± 1.7	4.3 ± 1.8	5.6 ± 1.6	0.018
Post-procedural hemodynamic						
SBP, mm Hg	136.61 ± 25.01	139.03 ± 23.35	136.03 ± 28.1	138.90 ± 26.8	134.8 ± 21.97	0.214
DBP, mm Hg	82.58 ± 12.39	82.83 ± 9.62	83.23 ± 16.03	82.3 ± 12.29	82.41 ± 11.23	0.616
HR, bpm	73.92 ± 13.14	71.03 ± 11.13	76.50 ± 15.22	72.93 ± 10.50	76.93 ± 13.74	0.080
LV EDV, mL	126.80 ± 29.93	119.70 ± 22.49	129.43 ± 24.01	130.21 ± 25.69	122.8 ± 28.20	0.062
LV ESV, mL	49.41 ± 7.81	54.47 ± 17.12	63.43 ± 20.55	66.13 ± 14.28	59.93 ± 18.30	0.040
LVEF, %	49.41 ± 7.81	53.07 ± 8.23	49.63 ± 9.01	46.89 ± 4.24	47.90 ± 7.31	0.016
GLS, %	–10.42 ± 2.54	–11.72 ± 1.76	–11.58 ± 1.93	–10.19 ± 2.63	–8.11 ± 1.91	0.022
E/e'	12.20 ± 4.25	10.02 ± 2.87	13.12 ± 4.52	12.65 ± 4.67	11.90 ± 3.92	0.024
iLAV, mL/m^2	17.53 ± 5.58	15.73 ± 5.63	16.55 ± 5.16	18.00 ± 3.88	18.91 ± 7.30	0.388
Adverse cardiac remodeling criteria						
ACR, n (%)	59 (49.6)	11 (36.7)	14 (6.7)	15 (56.0)	19 (65.6)	0.039
Biomarkers						
Peak troponin I, ng/mL [median (IQR)]	4.9 (1.4-7.8)	5.6 (1.8-7.5)	4.7 (2.3-6.4)	3.9 (1.4-7.2)	4.6 (2.1-7.8)	0.127
NT-proBNP, pg/mL [median, (IQR)]	753 (446–1120)	468 (288–616)	595 (390–774)	790 (420–1004)	982 (630–1260)	0.042
eGFR, mL/min/1.73m^2	78.16 ± 29.36	95.80 ± 38.11	76.50 ± 15.22	61.00 ± 21.38	85.53 ± 29.95	0.216
TC, mmol/L	4.96 ± 1.22	4.98 ± 1.09	5.21 ± 1.41	4.90 ± 1.30	4.92 ± 1.20	0.392
LDL-C, mmol/L	2.98 ± 1.09	2.87 ± 0.99	3.22 ± 1.35	3.03 ± 1.17	2.85 ± 0.71	0.328

(*Continued*)

Table 1. Characteristics of the Study Population Depending on Quartiles of LVMD (*Continued*)

Variables	Entire Group (n=119)	First Quartile (0-18 ms) (n=30)	Second Quartile (25-31 ms) (n=30)	Third Quartile (36-48 ms) (n=30)	Fourth Quartile (63-78 ms) (n=29)	*P*
HDL-C, mmol/L	1.04 ± 0.21	1.09 ± 0.19	1.05 ± 0.24	1.03 ± 0.24	1.01 ± 0.17	0.176
TG, mmol/L	1.95 ± 0.91	1.89 ± 1.16	1.94 ± 0.79	1.1 ± 0.71	1.92 ± 0.66	0.416
			Concomitant medications			
Aspirin, n (%)	119 (100)	30 (100)	30 (100)	30 (100)	29 (100)	0.98
Ticagrelor, n (%)	109 (91.6)	30 (100)	27 (90.0)	26 (86.7)	26 (89.7)	0.119
Clopidogrel, n (%)	11 (9.2)	0	3 (10.0)	4 (13.3)	4 (13.8)	0.119
Statins, n (%)	119 (100)	30 (100)	30 (100)	30 (100)	29 (100)	0.98
Beta-blockers, n (%)	99 (83.2)	25 (83.3)	27 (90.0)	21 (72.4)	26 (89.7)	0.180
ACEI/ARB, n (%)	116 (97.5)	29 (96.7)	30 (100)	28 (93.3)	29 (100)	0.500
MCA, n (%)	11 (9.2)	2 (6.7)	4 (13.3)	1 (3.3)	4 (13.8)	0.177

Variables of quartiles were compared using the Tukey's test.
ACEI, angiotensin-converting enzyme inhibitors; ACR, adverse cardiac remodeling; ARB, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; GRACE, Global Registry of Acute Coronary Events; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; iLAV, left atrium volume index; IQR, interquartile range; LAD, left artery descending artery; LDL-C, low-density lipoprotein cholesterol; LV EDV, left ventricular end-diastolic volume; LV ESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVMD, left ventricular mechanic dispersion; MCA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal fragment of brain natriuretic peptide; RCA, right coronary artery; SBP, systolic blood pressure; STEMI, ST segment elevation myocardial infarction; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; TIMI, thrombolysis in myocardial infarction.

Comparison of the Predictive Models

Table 3 illustrates the fact that the addition of LVMD to the based predictive model (NT-proBNP > 953 pg/mL) significantly improved the discriminative potency of the whole model, whereas GLS did not yield it. In addition, GLS and LVMD being added to the based model did not increase the predictive value of the based model constructed from NT-proBNP . Thus, LVMD became an independent predictor of ACR, which enabled to improve the discriminative potency of NT-proBNP.

Evaluation of Reproducibility

The evaluation of the reproducibility of longitudinal LVMD was performed in comparison with GLS. The intraclass correlation coefficient for inter-observer reproducibility of GLS was 0.89 (95% CI=0.85-0.93), whereas the intraclass correlation coefficient for intraobserver reproducibility of LVMD was 0.87 (95% CI=0.84-0.92).

Discussion

The study results clarified that the high quartile (Q4) of LVMD versus lowered quartiles of this parameter seemed to be an independent predictor of ACR and that addition of Q4 LVMD to the traditional predictive models shaped from NT-proBNP significantly improved the discriminative potency of the whole model. In addition, GLS > –8% was not considered to be

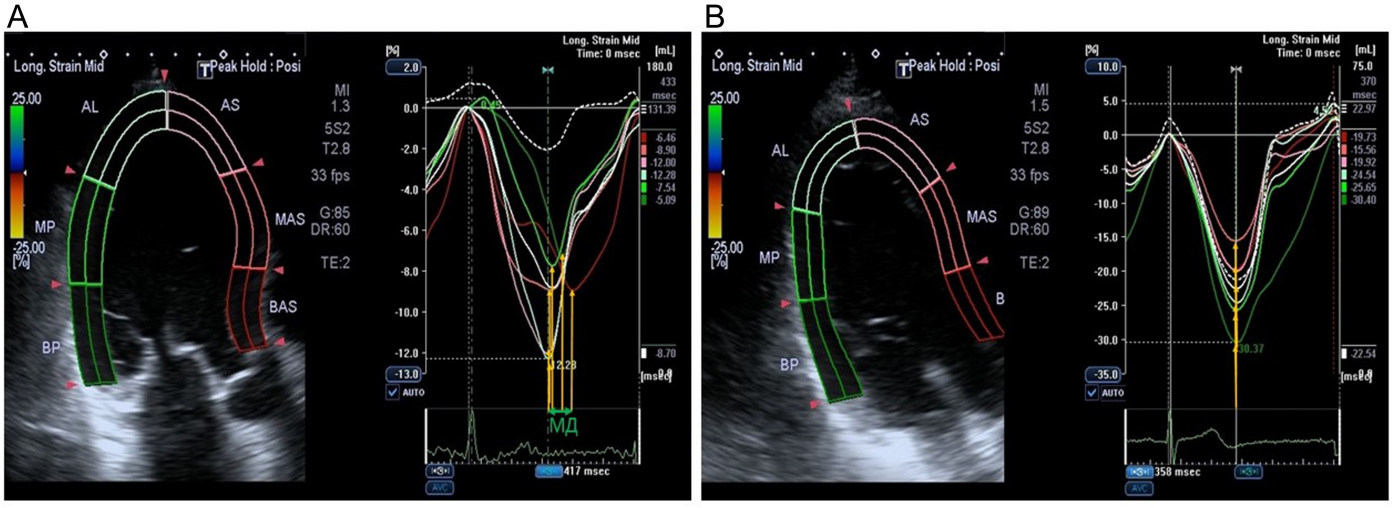

Figure 2. Typical changes in GLS in patients with and without LVMD. GLS, global longitudinal strain; LVMD, left ventricular mechanical dispersion. Yellow arrows point at the peak longitudinal strain in apical 3-chamber views. Green arrows define LVMD as the SD between the time measured from the beginning of the QRS complex to the peak longitudinal strain.

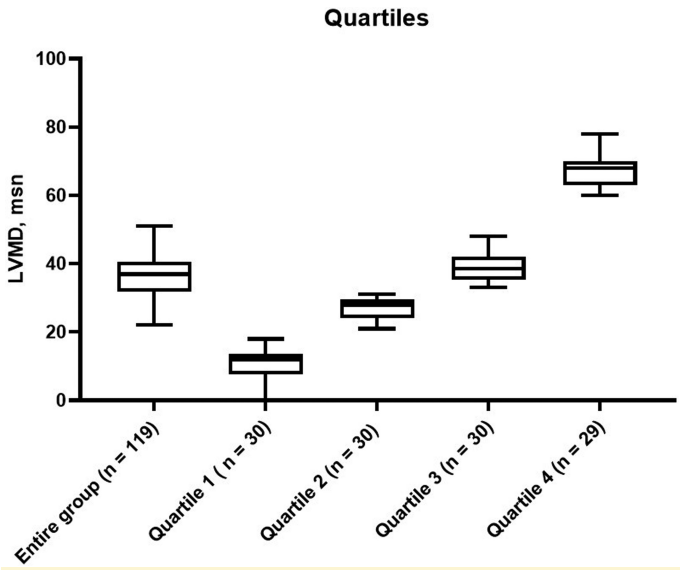

Figure 3. The quartiles of LVMD values in STEMI patients. LVMD, left ventricular mechanical dispersion; STEMI, ST segment elevation myocardial infarction.

powerful discriminator of the models based on NT-proBNP and Q4 LVMD. Pervious clinical studies revealed that LVMD assessed by 2D speckle-tracking echocardiography significantly increased depending on the severity of aortic stenosis,[29] T2DM-induced cardiomyopathy,[30] HF[31] dilated cardiomyopathy,[32] and ischemia cardiomyopathy.[33] Moreover, LVMD was significantly associated with all-cause mortality and CV mortality.[34,35] Little known about a predictive value of LVMD for STEMI patients undergoing primary of emergency PCI . De Sousa Bispo et al[36] in a small retrospective study (n=377) have clearly shown that in STEMI patients without previous ischemic events and LVEF 50 ± 10% prolonged LVMD > 52 ms had a sensitivity of 76% and a negative predictive value of 83% for mortality and hospitalization within 36-month follow-up period . Although these findings might not be interpolated to STEMI patients with successful revascularization by PCI and LVEF < 40%, the authors believe that LVMD is a promising prognostic biomarker for the risk stratification at discharge.[36] Abou et al[37] reported that an increase in LVMD was independently associated with the risk of all-cause mortality and had incremental predictive value for all-cause mortality over clinical and echocardiographic parameters. We also evaluated benefits of prolonged LVMD (Q4 vs. Q1-Q3) in the prediction of ACR in post-PCI STEMI patients without HFrEF at discharge and found that this parameter exerted a superiority when compared with traditionally used echocardiographic performances, as well as conventional risk scores, such as the GRACE and TIMI scores. Moreover, amongst patients enrolled in our study, LVMD improved the discriminative ability of the whole model based on a measurement of NT-proBNP. Thus, we first received resoundingly clear proof regarding the fact that profound prolongation of LVMD (Q4=63.0-78.0 ms) enables to improve the 365-day risk stratification of ACR regardless of other traditional parameters, including GLS and GRACE/TIMI scores.

In addition to this fact, there is evidence that in patients with stable coronary artery disease 1 year after successful coronary revascularization, prolonged LVMD unveiled the possibility to provide the incremental prognostic value for all-cause mortality, recurrent CV events, and hospitalization for acute myocardial infarction or HF when added to GLS, but not to NT-proBNP.[38] Yet, in patients with HFrEF, prolonged LVMD was found to be a more powerful predictor of ventricular arrhythmias than LVEF and GLS.[39] Collectively, this and other findings confirmed that LVMD was independently associated with myocardial remodeling and all-cause mortality.[14,39,40] In fact, the results of these studies tackled the discriminative value of LVMD for ACR, all-cause mortality, and HF-related hospital admission with reduced or mildly

Table 2. Factors Contributing Adverse Cardiac Remodeling in Post-PCI STEMI Patients: The Results of Univariate and Multivariate Log Regressions

	Depending Variable: ACR							
	Univariate Log Regressive Analysis				Multivariate Log Regressive Analysis			
Variables	*β*	**OR**	**95% CI**	***P***	*β*	**OR**	**95% CI**	***P***
GRACE score	2.32	1.08	1.02-3.32	0.018	2.30	1.04	1.01-2.75	0.064
TIMI score	1.25	1.07	1.00-1.18	0.410			–	
NT-proBNP	4.62	1.12	1.04-3.66	0.001	4.55	1.09	1.06-2.80	0.001
Peak TnI	3.43	1.09	1.05-2.37	0.001	3.26	1.04	1.00-1.90	0.670
T2DM	0.37	1.02	0.96-1.04	0.876			–	
Anterior STEMI	0.32	1.01	1.00-1.03	0.840			–	
eGFR	0.82	1.03	1.01-1.06	0.052			–	
LVEF	11.43	0.88	0.75-0.94	0.024	11.28	0.90	0.80-0.98	0.050
GLS	5.20	1.15	1.02-1.92	0.001	5.90	1.18	1.03-1.89	0.001
LVMD	13.70	1.32	1.06-2.42	0.001	14.20	1.34	1.04-2.17	0.001

ACR, adverse cardiac remodeling; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; LVMD, left ventricular mechanic dispersion; NT-proBNP, N-terminal fragment of brain natriuretic peptide; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; T2DM, type 2 diabetes mellitus; TIMI, thrombolysis in myocardial infarction; TnI, troponin I.

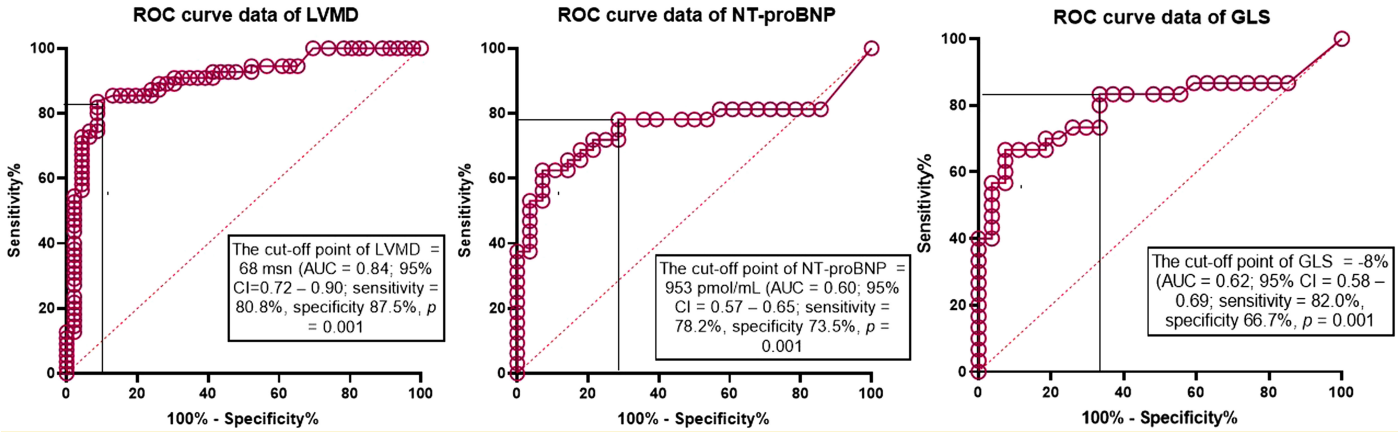

Figure 4. Receiver operating characteristic curves illustrate the reliability of predictive models constructed from LVMD, NT-proBNP, and GLS for ACR. ACR, adverse cardiac remodeling; AUC, area under the curve; GLS, global longitudinal strain; LVMD, left ventricular mechanical dispersion; NT-proBNP, N-terminal fragment of brain natriuretic peptide.

reduced LVEF. On the contrary, STEMI patients having normal or near-normal LVEF had not revealed the strong benefits of LVMD over GLS in the prediction of unfavorable clinical outcomes for 1-year period after PCI. Perhaps, there is a bias that related to a lack of scientific proof regarding the efficacy of primary PCI. Indeed, the current recommendation to restore effective blood flow through each ischemia-related stenosis of coronary arteries is not completely performed due to various reasons even in advanced PCI centers. Thus, a risk of the occurrence of early ACR, which is associated with altered GLS, is regarded to be higher in partial revascularization or in case of the microvascular obstruction than complete revascularization.[41,42]

Two-dimensional speckle-tracking echocardiography seems to be a useful tool for the early identification of local and global cardiac dysfunction, but it remains unclear whether GLS and/or LVMD represent equivocal predictive information in STEMI patients depending on LVEF and multiple coronary lesions.[43] We included STEMI patients who were effectively treated with PCI so that post-PCI TIMI flow grade was >2 who did not have reduced LVEF and found serious benefit for LVMD for ACR prediction when compared with GLS and circulating biomarkers, such as NT-proBNP. At the same time, these benefits were not translated to STEMI patients from the entire population but only those who had high quartile of LVMD. However, the predictive ability of Q4 LVMD was found to be higher than Q1-Q3 LVMD, NT-proBNP, and GLS, whereas GLS was not better than NT-proBNP. This is an illustration of the fact that the culprit lesions in STEMI patients with multivessel coronary artery disease being treated with complete revascularization strategy with PCI were particularly associated with microvascular inflammation and obstruction, which rather alter myocardial layer synchronism than impair global pump cardiac function.[44,45] Thus, we hypothesized that dual biomarker strategies based on measurements of both the levels of NT-proBNP and LVMD are very promising.

Study Limitations

The study has a small sample size as the first limitation, while we estimated the sample size through appropriate formula taking into consideration the sensitivity and specificity of LVMD in prediction of major CV events that had been recently received. Second, we did not include STEMI patients at high risk of untoward clinical course estimated by TIMI > 7, because it could have led to disproportionate inclusion in the study of the patients with highest quartile of LVMD. Third, we did not evaluate ongoing ischemia after revascularization that might intervene in the study group formation and impact indirectly on the results. The next limitation is a lack of validation of the new biomarker predictive model, but we will continue this evaluation in the near future with the aim of giving more comprehensive elucidation of the sensitivity and specificity of the model. In addition to this, we did not perform within the study period the coronary physiological assessment including direct measurement of fractional flow reserve to identify a significance of multiple-vessel disease to

Table 3. Statistics for Model Fit for the Prediction of ACR

	Depended Variable: ACR					
	AUC		NRI		IDI	
Predictive Models	**Median (95% CI)**	***P***	**Median (95% CI)**	***P***	**Median (95% CI)**	***P***
Model 1 (based model: NT-proBNP > 953 pg/mL)	0.60 (0.57-0.65)	–	Reference	–	Reference	
Model 2 (based model+GLS > –8%)	0.62 (0.58-0.69)	0.49	0.30	0.25	0.040	0.62
Model 3 (based model+LVMD Q4)	0.84 (0.72-0.90)	0.001	0.54	0.018	0.53	0.042
Model 4 (based model+GLS > –8% and LVMD Q4)	0.83 (0.73-0.91)	0.001	0.52	0.020	0.52	0.044

AUC, area under curve; ACR, adverse cardiac remodeling; GLS, global longitudinal strain; IDI, integrated discrimination indices; LVMD, left ventricular mechanical dispersion; NRI, net-reclassification improvement; NT-proBNP, N-terminal fragment of brain natriuretic peptide.

minimize the observer bias in visual estimation of coronary artery stenosis. Although PCI has been solely performed in connection with a visual estimation of ischemic risk per study protocol, highly experienced supervisors provided the procedure. Finally, we believe that these study limitations will not sufficiently curb the significance of the findings received.

Conclusion

High quartile (Q4) of LVMD exerted a higher predictive value of ACR than low quartiles (Q1-Q3), and the addition of Q4 LVMD to NT-proBNP significantly improved the cumulative discriminative potency of the model. Measurement of LVMD might be useful in determining the risk of adverse cardiac remodeling in post-PCI STEMI patients.

Data Availability: The data in this manuscript are available from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of L.T. Malaya National Therapy Institute of the National Academy of Medical Sciences of Ukraine (Approval No: 6, date: May 30, 2017).

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – O.V.P.; Design – O.V.P.; Supervision – M.P.K.; Materials – O.V.P., A.V.K.; Data Collection and/or Processing – A.V.K.; Analysis and/or Interpretation – A.V.K., A.E.B.; Literature Review – A.V.K., A.E.B; Writing – O.V.P., M.P.K., A.V.K., A.E.B.; Critical Review – O.V.P., M.P.K., A.E.B.

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Declaration of Interests: The authors declare that there were no conflicts of interest in the study.

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