The Prognostic Value of Lipoprotein-Associated Phospholipase A$_2$ in the Long-Term Care of Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Lijiao Yang[1], Hong Wang[1], Yida Zhang[1], Tingting Han[1], and Wenfeng Wang[1]

Abstract

Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is an independent risk factor for cardiovascular disease. Accordingly, studies from many countries around the world have shown an association between Lp-PLA$_2$ and cardiovascular events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), but this association has not been documented among the Chinese. The aim of this study was to assess the use of Lp-PLA$_2$ as a useful marker for predicting the long-term prognosis of Chinese patients with ACS undergoing PCI. A total of 651 consecutive patients undergoing PCI between September 2013 and January 2015 were divided into 2 groups: the high Lp-PLA$_2$ group (n = 262, Lp-PLA$_2$ > 138 nmol/L) and the low Lp-PLA$_2$ group (n = 389, Lp-PLA$_2$ $\leq$ 138 nmol/L). The end point was all-cause mortality and rehospitalization. The median follow-up was 24 months. Multivariate analysis showed that high Lp-PLA$_2$ was an independent predictor of all-cause mortality and rehospitalization (hazard ratio: 1.429, 95% confidence interval [CI]: 1.411-1.448; P < .05). The Lp-PLA$_2$ had good accuracy for predicting all-cause mortality and rehospitalization among patients with ACS undergoing PCI (area under the receiver–operating characteristic curve: 0.858, 95% CI: 0.819-0.898; P < .05), and a good correlation with the Global Registry of Acute Coronary Event score ($r = 0.525$, P < .05). This study provided evidence that Lp-PLA$_2$ could predict all-cause mortality and rehospitalization risk among patients with ACS undergoing PCI.

Keywords

lipoprotein-associated phospholipase A$_2$, Global Registry of Acute Coronary Event score, prognostic, acute coronary syndrome

Introduction

Cardiovascular disease is the leading cause of death globally. The major pathogenic mechanisms are atherosclerosis and thrombosis, in which inflammation plays a key role.[1] Accordingly, inflammation-based markers have been used to distinguish between patients and prognosticate based on risk profiles. Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is one of these markers that has come to be associated with a higher incidence of cardiovascular events and is a potential pathogenic factor participating in the progression of atherosclerosis.[2] Moreover, an increased Lp-PLA$_2$ is associated with coronary heart disease and ischemic stroke.[3-5] However, there is a scarcity of data regarding the relationship of Lp-PLA$_2$, coronary heart disease, and mortality in China. Besides Lp-PLA$_2$, other laboratory variables, such as mean platelet volume (MPV), platelet distribution width (PDW), serum uric acid (SUA), and

red blood cell distribution width (RDW), have also been associated with coronary heart disease.[6-10] The Global Registry of Acute Coronary Event (GRACE) risk stratification, as a clinical scoring system, can help us identify patients in high risk.[11,12] However, GRACE score is based on several clinical and laboratory variables that limit its use. Thus, it is necessary to find effective and easily obtainable biomarkers for predicting the prognosis of patients with acute coronary

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[1] Department of Cardiology, Affiliated Hospital of Chengde Medical College, Chengde, Hebei Province, China

Corresponding Author:
Hong Wang, Department of Cardiology, Affiliated Hospital of Chengde Medical College, No 36, Nanyingzi Street 067000, Chengde, Hebei Province, China.
Email: wanghong3721@163.com

Table 1. Baseline Clinical Characteristics.

	Low Lp-PLA$_2$ n = 389	High Lp-PLA$_2$ n = 262	P
Age (years)	58.4637 ± 9.86750	59.5988 ± 9.81092	.421
Male	309 (79.6%)	194 (74.1%)	.178
Hypertension	198 (50.9%)	147 (56.2%)	.279
Diabetes	92 (23.9%)	59 (22.8%)	.803
Current smokers	266 (68.5%)	176 (67.4%)	.418
Current drinking	215 (55.4%)	127 (48.8%)	.178
Family history of coronary artery disease	56 (14.5%)	43 (16.7%)	.546
Systolic blood pressure at admission, mm Hg	134.5329 ± 27.51704	132.2099 ± 24.87894	.374
Diastolic blood pressure at admission, mm Hg	91.2249 ± 25.35665	89.8765 ± 23.97353	.581
Heart rate at admission, beat/min	77.0796 ± 14.37532	74.6605 ± 14.12375	.085
White blood cell count (×10^9/L)	8.3941 ± 3.03649	8.7049 ± 3.21393	.316
Red blood cell count (×10^9/L)	4.7210 ± 0.53988	4.7329 ± 0.50896	.816
Hemoglobin (g/dL)	147.8097 ± 17.25669	145.9691 ± 16.27345	.268
Platelet count (×10^9/L)	221.9170 ± 51.46527	223.7346 ± 56.02371	.728
Neutrophil ratio (%)	68.6454 ± 12.04808	69.4380 ± 12.35699	.510
Lymphocyte ratio (%)	24.0851 ± 15.73070	24.1210 ± 10.23206	.979
Monocytes ratio (%)	5.5353 ± 2.52088	5.2895 ± 1.96357	.284
Neutrophil count (× 10^9/L)	5.9693 ± 3.08614	6.2421 ± 3.16082	.376
Lymphocyte count (× 10^9/L)	1.8768 ± 0.84004	1.8450 ± 0.76647	.691
Monocytes count (× 10^9/L)	0.4815 ± 0.51408	0.4344 ± 0.20216	.264
MPV	10.4009 ± 0.95262	10.5607 ± 1.01578	.096
PDW	12.1277 ± 1.99137	12.1895 ± 2.00507	.752
RDW	42.4754 ± 2.79236	42.5759 ± 3.00136	.721
Serum creatinine (mg/dL)	69.7119 ± 14.57290	70.2575 ± 17.84405	.726
SUA	328.3471 ± 71.52341	334.5222 ± 77.77927	.395
TG	2.1734 ± 1.83701	2.2675 ± 1.88345	.605
HDL	1.0074 ± 0.29495	0.9560 ± 0.24446	.060
LDL	2.1826 ± 0.93202	2.2598 ± 0.84720	.371
ApoA	1.1626 ± 0.35283	1.2375 ± 0.84511	.189
ApoB	0.8193 ± 0.26398	0.8082 ± 0.28721	.679
Serum potassium at admission	3.8790 ± 0.41051	3.9444 ± 0.41953	.108
LVEF (%)	56.6920 ± 7.87656	57.7469 ± 8.79533	.192
Killip class ≥2 at admission	24 (6.2%)	17 (6.8%)	.816
GRACE score	121.3529 ± 24.39931	141.4444 ± 29.44982	0.000
Emergency PCI	167 (43.0%)	114 (43.8%)	.413
Left main artery	8 (2.1%)	11 (4.3%)	.172
Number of lesion vessels	2.0450 ± 0.87483	2.1790 ± 0.91844	.126
TIMI flow grade 0/1 before PCI	81 (28.0%)	68 (42.0%)	.003
Use of glycoprotein IIb/IIIa inhibitor	153 (52.9%)	102 (63.0%)	.039
Antithrombotic drugs			
Aspirin	382 (98.2%)	259 (98.7%)	.08
Clopidogrel	381 (98.0%)	260 (99.4%)	.204
PCI with stent implantation	387 (99.5%)	260 (99.2%)	.884
PCI without stent implantation	2 (0.5%)	2 (0.8%)	.892

Note: "±"is used to express the fluctuation of measurement data.
Abbreviations: MPV, mean platelet volume; PDW, platelet distribution width; RDW, red blood cell distribution width; SUA, serum uric acid; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA, lipoprotein(a); ApoB, lipoprotein(b); PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction.

syndrome (ACS). Therefore, the aim of this study was to assess Lp-PLA$_2$ an effective marker for predicting the long-term prognosis of Chinese patients with ACS undergoing percutaneous coronary intervention (PCI).

Methods

This study was a prospective study among all patients with ACS who were hospitalized and underwent PCI at the Affiliated Hospital of Chengde Medical College. A total of 651 patients were selected between September 2013 and January 2015 in this large-scale hospital study in Northwest China. Initially, all consecutive patients undergoing PCI were identified from Picture Archiving and Communication Systems and were assigned a unique study ID. Then, patients' information were recorded, including demographic and clinical characteristics, and laboratory measurements. Additionally, each patient was mandated to sign an informed consent agreement before

enrollment, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Left ventricular ejection fraction was measured by echocardiography using the biplane method of discs during hospitalization.[13] A computer analysis system was used to estimate the angiographic characteristics, while thrombolysis in myocardial infarction (TIMI) flow grade was determined as previously defined.[14] The GRACE score was calculated at admission, and only patients with intact GRACE score variables were enrolled in the present study. All other events were obtained from the patients' medical records and from the patients by telephone interview and/or outpatient clinic visits. All patients were followed up for a mean duration of 24 months.

All cases underwent blood testing and clinical examination, during which blood samples were taken from a peripheral vein after an overnight fast for the measurement of laboratory variables including MPV, PDW, SUA, RDW, triglyceride, low-density lipoprotein, high-density lipoprotein, lipoprotein(a), and lipoprotein(b). Blood samples for the measurement of Lp-PLA$_2$ were taken from a peripheral artery before coronary angiography, and the nonheparinized blood serum was segregated and stored at $-80°C$ for further detection. The Lp-PLA$_2$ was detected by enzyme-linked immunosorbent assay.

According to current guidelines, unstable angina patients were identified based on ischemic symptoms suggestive of ACS without electrocardiogram changes indicating ischemia. Thus, non-ST-elevation myocardial infarction (NSTE-MI) was defined as no ST elevation in electrocardiograms but with an increase in cardiac ischemia markers, while STE-MI was defined as patients with typical ischemic chest pain lasting more than 20 minutes along with 1 of the following criteria: at least 1 mm ST elevation, the elevation of cardiac markers at least twice the maximum normal values. After confirmation of ACS, PCI was undertaken according to current guideline recommendation. The use of aspiration thrombectomy, heparin, or glycoprotein IIb/IIIa inhibitor was decided by the operators. All patients received standard care according to the current guidelines.[12,15] Exclusion criteria included (1) coronary artery bypass grafting, (2) active infection, (3) hematological disorders, (4) severe liver or renal disease, (5) autoimmune disease or steroid therapy, and (6) no blood sample before coronary angiography or unavailability of GRACE score.

The clinical end points were defined as the composite of all-cause mortality and rehospitalization during the follow-up period. All end points were based on standardized definitions.[16]

Statistical analyses for this study are as follows: Quantitative variables with normal distribution were expressed as mean (standard deviation), and those with nonnormal distribution were expressed as median (interquartile range). Comparisons of parametric values were done by independent sample *t* test, while comparisons of nonparametric values were done using Mann-Whitney *U* test. Categorical variables were represented as counts and percentages (%) and were compared by the χ^2

Table 2. Correlation Analyses of Lp-PLA$_2$ Levels With Other Variables.

	r	*P*
GRACE score	0.525	.000
MPV	0.095	.044
SUA	0.123	.009
Age	0.233	.000
TIMI flow grade 0/1 before PCI	-0.123	.009

Abbreviations: Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; GRACE, Global Registry of Acute Coronary Event; MPV, mean platelet volume; SUA, serum uric acid; TIMI, thrombolysis in myocardial infarction.

Table 3. Multivariate Logistic Regression Analysis to Identify the Independent Predictors of Cardiovascular Events.

	Multivariate Analysis		
Variable	Odds Ratio	95% CI	*P*
GRACE score	1.013	1.002-1.025	.025
Lp-PLA$_2$	1.429	1.411-1.448	<.001
MPV	1.371	1.034-1.818	.028
Killip class $\geq$2 at admission	0.147	0.058-0.369	<.001

Abbreviations: GRACE, Global Registry of Acute Coronary Event; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MPV, mean platelet volume.

test or Fisher exact test. Correlation analyses of 2 quantitative variables with normal distribution were performed by linear correlation, while coefficient of correlation was expressed using Pearson and other correlation between variables was expressed by Spearman. In addition, multiple regression and logistic regression were used to identify independent predictors of high-risk patients. Kaplan-Meier was used to analyze the univariate effect on event-free survival and was tested by log rank ($P < .05$). Cox proportional hazards regression modeling was used to analyze the multivariate effect of variables on event-free survival. The variables that showed significance in univariate analysis ($P < .05$) and other variables known to affect prognosis after ACS were "entered" into the model. Results were expressed as hazard ratios (HRs) with associated 95% confidence intervals (CIs). The area under the receiver–operating characteristic curve (ROC-AUC) was used to assess the predictive value and calculate the cutoff of Lp-PLA$_2$. All tests were 2 sided, and the statistical significance was defined as $P < .05$. All statistical analyses were performed using SPSS version 19 (SPSS Inc, Chicago, Illinois).

Results

Baseline clinical characteristics of the population (n = 651), among whom 262 had high Lp-PLA$_2$ while 389 had low Lp-PLA$_2$, are listed in Table 1. Patients with high Lp-PLA$_2$ had significantly higher GRACE scores than those with low Lp-PLA$_2$ (Table 1). The rates of TIMI flow grade 0/1 before PCI use of glycoprotein IIb/IIIa inhibitor were found to be significantly higher in the high Lp-PLA$_2$ group (Table 1).
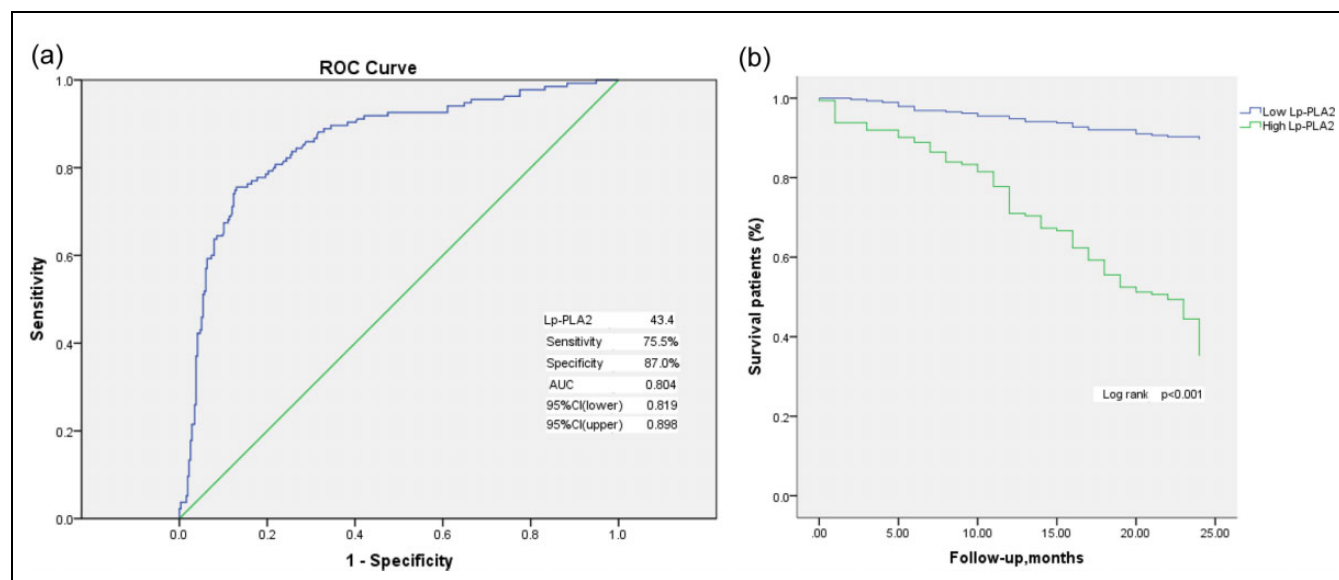
Figure 1. Receiver–operating characteristic curve.

Table 4. Variables Associated With Cardiovascular Events in Patients With ACS Under PCI From Kaplan-Meier and Cox Proportional Regression Analysis.

Variables	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Lp-LPA$_2$	1.332 (1.326-1.337)	<.001	1.329 (1.323-1.335)	<.001
GRACE score	1.016 (1.011-1.021)	<.001	1.007 (1.002-1.012)	.007
MPV	1.280 (1.089-1.506)	.003		
Age	1.023 (1.005-1.041)	.012		
Number of lesion vessels	1.356 (1.118-1.643)	.002		
Killip class ≥2 at admission	0.389 (0.237-0.639)	<.001	0.436 (0.250-0.761)	.003

Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; GRACE, Global Registry of Acute Coronary Event; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MPV, mean platelet volume; HR, hazard ratio; CI, confidence interval.

Subsequently, using Pearson or Spearman correlation coefficient, we estimated the correlation of Lp-PLA$_2$ with clinical characteristics and found a significant correlation between Lp-PLA$_2$ and GRACE score ($r = 0.525$, $P < .05$; Table 2).

Logistic regression was used to detect the independent risk factors for cardiovascular events in patients with ACS after PCI. After multivariate analysis, in addition to the GRACE score, MPV, and Killip class ≥2 at admission ($P < .05$), Lp-PLA$_2$ was found to be an independent risk factor (odds ratio: 1.429, 95% CI: 1.411-1.448; $P < .05$; Table 3).

The ROC curve analysis was used to assess predictive value of variables. The results demonstrated that Lp-PLA$_2$ (AUC: 0.858, 95% CI: 0.819-0.898; $P < .05$), GRACE score (AUC: 0.683, 95% CI: 0.628-0.738; $P < .05$), MPV (AUC: 0.583, 95% CI: 0.525-0.641; $P < .05$), and age (AUC: 0.580, 95% CI: 0.523-0.636; $P < .05$) were significant for prognostication. Furthermore, the ROC curve analysis was used to determine the cutoff value of Lp-PLA$_2$ to predict cardiovascular events, which was found to be 43.4, with 75.5% sensitivity and 87.0% specificity (Figure 1).

In the overall study population, univariate Kaplan-Meier survival analysis indicated that Lp-PLA$_2$ (HR: 1.332, 95% CI: 1.326-1.337; $P < .05$; Figure 1(b)) GRACE score (HR: 1.016, 95% CI: 1.011-1.021; $P < .05$), MPV (HR: 1.280, 95% CI: 1.089-1.506; $P < .05$), age (HR: 1.023, 95% CI: 1.005-1.041; $P < .05$), number of lesion vessels (HR: 1.356, 95% CI: 1.118-1.643; $P < .05$), and Killip class ≥2 at admission (HR: 0.389, 95% CI: 0.237-0.639, $P < .05$) were associated with greater cardiovascular events. Similarly, multivariate Cox proportional regression analyses (Table 4) showed that the major factors associated with increased cardiovascular events were Lp-PLA$_2$ (HR: 1.329, 95% CI: 1.323-1.335; $P < .05$), GRACE score (HR: 1.007, 95% CI: 1.002-1.012; $P < .05$), and Killip class ≥2 at admission (HR: 0.436, 95% CI: 0.250-0.761; $P < .05$).

Discussion

In the present study, we tested the predictive value of Lp-PLA$_2$ on the long-term prognosis of Chinese patients with ACS undergoing PCI. The main findings were as follows: (1) high Lp-PLA$_2$ was an independent predictor of all-cause mortality and rehospitalization among Chinese patients, (2) Lp-PLA$_2$ had good accuracy for predicting all-cause mortality and

rehospitalization in Chinese patients with ACS undergoing PCI, and (3) Lp-PLA$_2$ had a good correlation with GRACE score among these patients.

Coronary artery disease is the most prevalent manifestation of cardiovascular disease. It is necessary to distinguish the high-risk patients and take effective measures to reduce the associated mortality and improve cardiac function. The Lp-PLA$_2$, encoded by the *PLA2G7* gene, hydrolyzes oxidized phosphatidylcholine to release oxidized nonesterified fatty acid lysophosphatidylcholine. Elevated Lp-PLA$_2$ has been proposed as a specific indicator of cardiovascular events.[17,18] Our study was in good agreement with other reports that have shown that high Lp-PLA$_2$ was an independent predictor of all-cause mortality and rehospitalization. Additionally, GRACE score plays an important role in helping doctors recognize high-risk patients and take active measures to reduce cardiovascular disease.[19] In this study, our analysis showed that Lp-PLA$_2$ had a significant correlation with GRACE score. The ROC curve analysis indicated that Lp-PLA$_2$ was a good factor (AUC: 0.858) for predicting all-cause mortality and rehospitalization in Chinese patients with ACS undergoing PCI. The MPV is a link between thrombosis and inflammation, which reflects thrombogenesis and active platelets. Many observations had noted that MPV was a strong and independent predictor of mortality in patients with ACS.[20] However, some analysis confirmed that a higher baseline platelet count was a predictor of adverse prognosis or had no significant association in patients undergoing PCI.[21,22] Conversely, in our study, Kaplan-Meier curve showed that MPV (HR: 1.280, 95% CI: 1.089-1.506, $P = .003$) was associated with cardiovascular events in patients with ACS under PCI, but it was excluded from the Cox proportional regression analysis.

Furthermore, in our study, Lp-PLA$_2$ was shown to have significant correlation with variables associated with cardiovascular disease including GRACE score, MPV, SUA, and age, and had good performance for predicting all-cause mortality and rehospitalization in patients with ACS undergoing PCI. In aggregate, considering the results presented, it is worth emphasizing the prognostic value of Lp-PLA$_2$ in Chinese patients with ACS undergoing PCI.

Limitations

This clinical study had several limitations. First, our study was a single-center observational study, with potential confounders and selection bias that may not have been completely adjusted for. Second, there was a lack of data about the history of antiplatelet drugs use. In addition, not all of the rehospitalization patients underwent coronary angiography.

Conclusion

The Lp-PLA$_2$ could predict all-cause mortality and rehospitalization in Chinese patients with ACS undergoing PCI and had a significant correlation with GRACE score.

References

1. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med*. 2013;368(21): 2004-2013. doi: 10.1056/NEJMra1216063.
2. Colley KJ, Wolfert RL, Cobble ME. Lipoprotein-associated phospholipase A(2): role in atherosclerosis and utility as a biomarker for cardiovascular risk. *EPMA J* 2011;2(1):27-38. doi: 10.1007/s13167-011-0063-4.
3. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 2000;343(16):1148-1155. doi: 10.1056/NEJM200010193431603.
4. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities(ARIC) study. *Circulation*. 2004;109(7):837-842. doi: 10.1161/01.CIR.0000116763.91992.F1.
5. Epps KC, Wilensky RL. LP-PLA a novel risk factor for high-risk coronary and carotid artery disease. *J Intern Med*. 2011;269(1): 94-106. doi: 10.1111/j.1365-2796.2010.02297.x.
6. Sansanayudh N, Anothaisintawee T, Muntham D, McEvoy M, Attia J, Thakkinstian A. Mean platelet volume and coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol*. 2014;75(3):433-440. doi: 10.1016/j.ijcard.2014.06.028.
7. Ki YJ, Park S, Ha SL, et al. Usefulness of mean platelet volume as a biomarker for long-term clinical outcomes after percutaneous coronary intervention in Korea cohort: a comparable and additive predictive value to high-sensitivity cardiac troponin T and N-terminal pro-B type natriuretic peptide. *Platelets*. 2014;25(6): 427-432. doi: 10.3109/09537104.2013.835393.
8. Bekler A, Ozkan MT, Tenekecioglu E, et al. Increased platelet distribution width is associated with severity of coronary artery disease in patients with acute coronary syndrome. *Angiology*. 2015;66(7):638-643. doi: 10.1177/0003319714545779.
9. Zhao G, Huang L, Song M, Song Y. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies.

Atherosclerosis. 2013;231(1):61-68. doi: 10.1016/j.atherosclerosis.2013.08.023.

10. Lippi G, Filippozzi L, Montagnana M, et al. Clinical usefulness of measuring red blood cell distribution width on admission in patients with acute coronary syndromes. *Clin Chem Lab Med.* 2009;47(3):353-357.PMID:19676148.

11. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ.* 2006;333(7578)1091. doi: 10.1136/bmj.38985.646481.55.

12. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* 2016;37(3):267-315.

13. Lang RM, Bierig M, Devereux RB, et al; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7(2):79-108.

14. Sheehan FH, Braunwald E, Canner P, et al. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the thrombolysis in myocardial infarction (TIMI Phase I) trial. *Circulation.* 1987;75(4):817-829. PMID: 3103950.

15. O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol.* 2013;61(4):e78-e140.

16. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115(17):2344-2351.

17. Gregson J, Stirnadel-Farrant HA, Doobaree IU, Koro C. Variation of lipoprotein associated phospholipase A2 across demographic characteristics and cardiovascular risk factors: a systematic review of the literature. *Atherosclerosis.* 2012;225(1):11-21. doi: 10.1016/j.Atherosclerosis.2012.06.020.

18. Ridker PM, MacFadyen JG, Wolfert RL, Koenig W. Relationship of lipoprotein-associated phospholipase A_2 mass and activity with incident vascular events among primary prevention patients allocated to placebo or to statin therapy: an analysis from the JUPITER trial. *Clin Chem.* 2012;58(5):877-886. doi: 10.1373/clinchem.2011.180281.

19. Elbarouni B, Goodman SG, Yan RT, et al. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. *Am Heart J.* 2009;158(3):392-399. doi: 10.1016/j.ahj.2009.06.010.

20. Wasilewski J, Desperak P, Hawranek M, et al. Prognostic implications of mean platelet volume on short-and long-term outcomes among patients with non-ST-segment elevation myocardial infarction treated with percutaneous coronary intervention: a single-center large observational study. *Platelets.* 2016;27(5):452-458. doi: 10.3109/09537104.2016.1143919.

21. Nikolsky E, Grines CL, Cox DA, et al. Impact of baseline platelet count in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction (from the CADILLAC trial). *Am Heart J.* 2007;99(8):1055-1061. doi: 10.1016/j.amjcard.2006.11.066.

22. Tekbas E, Kara AF, Ariturk Z, et al. Mean platelet volume in predicting short-and long-term morbidity and mortality in patients with or without ST-segment elevation myocardial infarction. *Scand J Clin Lab Invest.* 2011;71(7):613-619. doi: 10.3109/0036-5513.2011.599416.