Původní sdělení | Original research article

Prognostic value of the combination of TIMI risk score and mean platelet volume to lymphocyte count ratio in patients with acute coronary syndrome

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Klíčová slova:
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Mortalita
Poměr průměrného objemu krevních destiček a počtu lymfocytů
Skórovací systém Thrombolysis In Myocardial Infarction

SOUHRN

Kontext: Hodnoty skórovacího systému Thrombolysis In Myocardial Infarction (TIMI) a poměru průměrného objemu krevních destiček (mean platelet volume, MPV) k počtu lymfocytů (lymphocyte ratio, MPVLR) představují významné parametry, jež lze použít k predikci mortality a vzniku závažných nežádoucích kardiovaskulárních příhod (major cardiovascular adverse events, MACE) u pacientů s akutním koronárním syndromem (AKS). Nicméně prognostická hodnota modifikovaného skórovacího systému založeného na vztazích a kombinacích těchto parametrů u pacientů s AKS není známa. Proto jsme se rozhodli prozkoumat vztah mezi modifikovaným rizikovým skóre získaným kombinací skórovacího systému TIMI a MPVLR v průběhu dvouletého sledování výskytu MACE a mortality u pacientů s AKS.
Metoda: Do naší studie bylo zařazeno 472 po sobě následujících pacientů s diagnózou AKS, léčených perkutánní koronární intervencí. Pacienti byli hodnoceni ve dvou skupinách, jednak MACE (+) a MACE (–), za druhé jako „vysoká" a „nízká" podle mezní hodnoty modifikovaného skóre MPVLR + TIMI.
Výsledky: Hodnoty ploch pod křivkami modifikovaného skóre MPVLR + TIMI pro dvouletou predikci výskytu MACE a mortality činily 0,893 (0,812–0,974; $p < 0,001$), resp. 0,864 (0,715–1,00; $p = 0,001$); přitom byly přesnější než hodnoty MPVLR a skóre TIMI samostatně. Analýza přežití při použití Kaplanovy–Meierovy metody prokázala, že kombinované skóre MPVLR + TIMI při dlouhodobém sledování incidence MACE a mortality (log rank test: 59,329; $p < 0,001$, resp. log rank test: 12,085; $p = 0,001$) je přesnější než jednotlivé hodnoty skóre MPVLR a TIMI. V Coxově regresní analýze provedené s cílem určit faktory dlouhodobého rizika pro vznik MACE se ukázalo, že kombinované skóre MPVLR + TIMI (HR: 5,41; $p = 0,006$) je přesnější než hodnota MPVLR (HR: 2,88; $p = 0,094$), skóre TIMI (HR: 2,92; $p = 0,099$) a další proměnné.
Závěr: Studie prokázala, že modifikované skóre MPVLR + TIMI je v predikci dvouleté mortality a incidence MACE u pacientů s AKS přesnější než hodnoty MPVLR a skóre TIMI použité samostatně.

Keywords:
Acute coronary syndrome
MACE
Mean platelet volume to lymphocyte ratio
Mortality
Thrombolysis In Myocardial Infarction risk score

ABSTRACT

Background: Thrombolysis In Myocardial Infarction (TIMI) risk score and MPV/lymphocyte ratio (MPVLR) are important parameters that can be used to predict mortality and major cardiovascular adverse events (MACE) in patients with acute coronary syndrome (ACS). However, the prognostic value of a modified score system that is based on the relationships and combinations of these parameters in ACS patients is unknown. Hence, we aimed to investigate the relationship between the modified risk score obtained by the combination of TIMI risk score and MPVLR with 2-year-long MACE and mortality in ACS patients.
Method: In this study, 472 consecutive patients with a diagnosis of ACS, who were revascularized using percutaneous coronary intervention, were included. The patients were evaluated in groups of two, namely MACE (+) and MACE (–), and also as "High" and "Low" according to the cut-off value of the MPVLR + TIMI modified score.
Results: The area under the curve values of the modified MPVLR + TIMI for two-year MACE and mortality prediction were found to be 0.893 (0.812–0.974, $p < 0.001$) and 0.864 (0.715–1.00, $p = 0.001$), respectively, and were observed to be superior to the individual MPVLR and TIMI scores. In the Kaplan–Meier survival analysis, it was detected that the MPVLR + TIMI combination score for long-term MACE and mortality (log rank: 59.329, $p < 0.001$ and log rank: 12.085, $p = 0.001$, respectively) was superior to individual MPVLR and TIMI scores. In the Cox regression analysis performed to determine long-term MACE risk factors, the MPVLR + TIMI combination score (HR: 5.41, $p = 0.006$) was noted to be superior to MPVLR (HR: 2.88, $p = 0.094$), TIMI score (HR: 2.92, $p = 0.099$), and other variables.
Conclusion: The modified MPVLR + TIMI score was found to be superior to the MPVLR and TIMI score individually in predicting 2-year mortality and MACE in ACS patients.

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Introduction

Acute myocardial infarction is one of the most common fatal clinical emergencies causing myocardial ischemic necrosis in which coronary blood flow is interrupted by thrombosis mechanisms.[1,2] Early risk classification and identification of high-risk patients with acute coronary syndrome (ACS) follow-up is of great importance in guiding prognosis, differential diagnosis, and treatment decisions. Hence, many risk identification scores based on the clinical history, vital signs at emergency admission, electrocardiography, and laboratory results of the patients were generated. Thrombolysis In Myocardial Infarction (TIMI) risk score is a useful tool that is frequently preferred among the various scoring systems and can be easily applied in clinical practice.[3] The TIMI risk score has been associated with mortality and cardiovascular adverse events in patients with non-ST elevation myocardial infarction (NSTEMI) with different designs in the literature.[3–6] Platelet activation plays an important role in the formation and progression of atherosclerosis and thrombus formation on ruptured atherosclerotic plaques.[7,8] It has been found that the increase in mean platelet volume (MPV) also accentuates the activation and aggregation of platelets.[9] Inflammation and thrombosis play an important role in the processthat results in atherosclerotic plaque formation, progression, destabilization, rupture, and thrombosis.[10] In the inflammation mechanism, lymphocytes accompany platelets that are involved in inflammation along with thrombosis.[11] Lymphocytes are one of the earliest cell types implicated in atherosclerotic plaque formation, and the reduction in their numbers is linked to an increased inflammatory response and contributes to the destabilization of plaques.[12] MPV is an easily accessible parameter obtained from routine hemogram data and it provides information about platelet activation and aggregation.[13,14] MPV/lymphocyte count ratio (MPVLR), which can provide details of thrombosis and inflamation, has become a valuable parameter attracting the attention of clinicians in the literature. MPVLR has been associated with cardiovascular mortality and adverse events as well as survival even in patients with non-metastatic clear cell renal cell carcinoma who underwent nephrectomy.[13–15] However, there are no studies in the literature which evaluate the relationship between MPVLR and TIMI score and the combination of MPVLR with TIMI score in the prognosis of patients with ACS revascularized by percutaneous coronary intervention (PCI). This study aimed to evaluate the possible relationship between MPVLR and TIMI score and to investigate whether the combined MPVLR and TIMI score is a strong predictor of 2-year major adverse cardiovascular events (MACE) in patients with ACS who had undergone PCI for revascularization.

Materials and methods

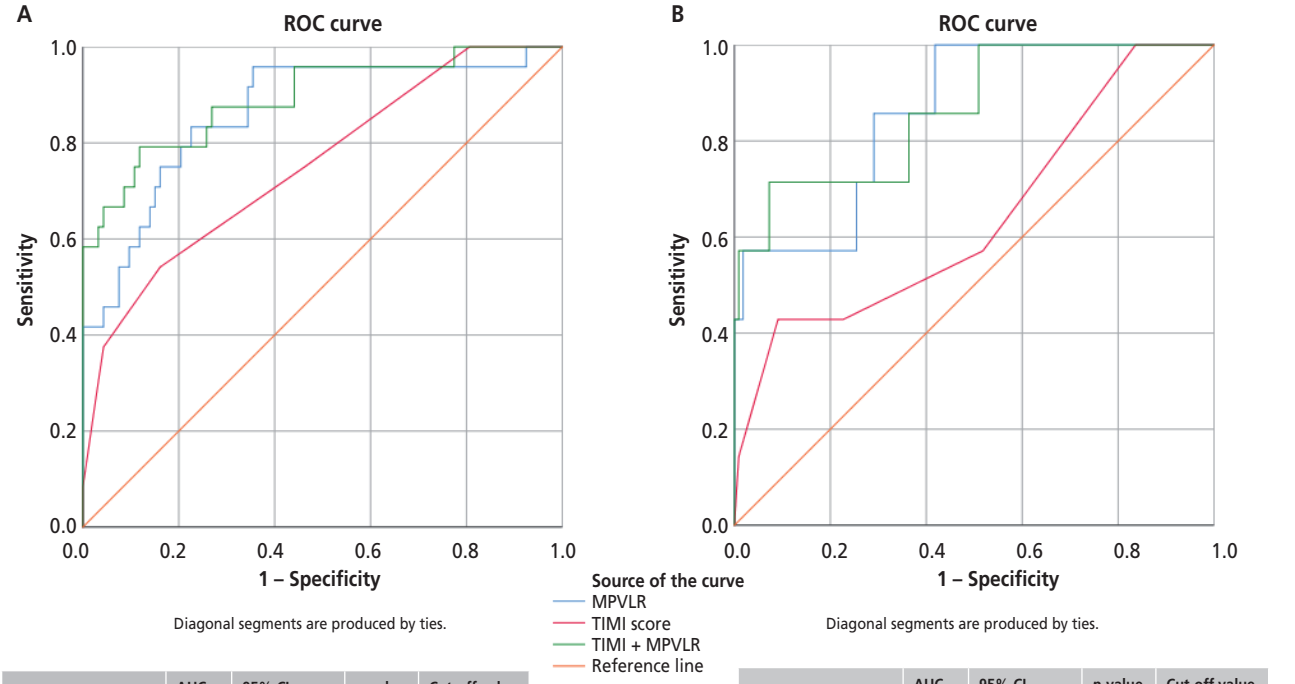
In our study, 856 consecutive ACS patients who had undergone PCI between October 2018 and March 2019 were retrospectively assessed. Under the title of acute coronary syndrome, patients without NSTEMI and unstable angina pectoris (USAP) were evaluated. According to our exclusion criteria, patients with autoimmune diseases (n = 16), those with congenital heart disease (n = 16), those undergoing cancer treatment (n = 20), those with acute or chronic inflammatory diseases (n = 24), those with advanced renal dysfunction (n = 24), those who had received or were receiving steroid therapy within the last 3 months (n = 20), those who had a history of myocardial infarction and/or PCI (n = 96), and those who were under medical follow-up without undergoing coronary angiography due to advanced age and additional comorbidities (n = 60), those who were referred for coronary artery bypass graft surgery following diagnostic angiography (n = 76), and those with incomplete data or were unreachable (n = 32) were excluded from the study. Finally, 472 patients were included in the study. The study was conducted in accordance with the Declaration of Helsinki principles and with the approval of the local ethics committee.

Demographic data of the study patients were recorded, and their venous blood samples were routinely taken before percutaneous coronary interventions. Hematological analyses such as lymphocyte count, platelet count, hemoglobin, and MPV were performed. Complete blood counts were carried out with the XT-4000 automatic hematological analysis system (Sysmex Corporation). Furthermore, biochemical parameters such as creatinine and glomerular filtration rate (GFR) were checked in our study. GFR was calculated using the MDRD (Modification of Diet in Renal Diseases Study) formula (http://www.tsn.org.tr/formul.php).

MPVLR, which was previously proven to be associated with cardiovascular mortality and morbidity, was calculated using the results obtained from the first complete blood count at the admission to the hospital. MPVLR was defined as the ratio of MPV to the number of lymphocytes.[16] SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) scores of the study patients were obtained using a web-based calculation system (http://www.syntaxscore.com). Using a computer program on the national chest pain center platform (https://datacs.chinacpc.org), the first attending physician recorded the Global Registry of Acute Coronary Events (GRACE) scores of all the patients at admission. Demographic data and variables determined Thrombolysis in Myocardial Infarction (TIMI) risk score points. The TIMI score for NSTEMI and UA involves patient age, risk factors for coronary artery disease (hypertension, dyslipidemia, diabetes mellitus, active smoking, and heredity for coronary disease), prior coronary stenosis of 50% or more, use of acetylsalicylates in the previous seven days, at least 2 angina events in the previous 24 hours, increased serum cardiac biomarkers, and ST-segment deviation on ECG at presentation. The score of seven points is an important predictor of the development of adverse events such as new MI or REMI, death or severe recurrent ischemia requiring urgent revascularization.[3] The TIMI risk score was also obtained by an online calculation tool in accordance with the literature (https//www.mdcalc.com/timi-risk-score-ua-nsvesi#next-steps).[3]

Primary endpoint and follow-up

Follow-up up of patients was completed by reviewing hospital records, outpatient visits, and telephone contact.



	AUC	95% CI	*p*-value	Cut-off value
MPVLR	0.864	0.777–0.952	0.000	4.71
TIMI score	0.753	0.641–0.865	0.000	4.50
MPVLR + TIMI score	0.893	0.812–0.974	0.000	9.59

	AUC	95% CI	*p*-value	Cut-off value
MPVLR	0.860	0.733–0.987	0.001	4.28
TIMI score	0.642	0.410–0.873	0.210	5.50
MPVLR + TIMI score	0.864	0.715–1.000	0.001	10.75

Fig. 1 – Receiver operating characteristic curves presenting AUC values for MPVLR alone, TIMI score alone and MPVLR in combination with TIMI score (MPVLR + TIMI). (A) 2-year MACE and (B) 2-year mortality were predicted in patients with ACS. AUC – area under the curve; CI – confidence ınterval; MACE – major adverse cardiovascular events; MPVLR – mean platelet volume to lymphocyte ratio; TIMI – Thrombolysis In Myocardial Infarction.

The main outcome was that major advers cardiovascular events (MACE) occurred during the follow-up period. MACE included: cardiogenic or all-cause mortality, malignant arrhythmias (ventricular tachycardia, ventricular fibrillation, grade III atrioventricular block), recurrent myocardial infarction, recurrent angina, acute heart failure and stroke (neurological disorders related to recent ischemic or hemorrhagic events).

The patients were evaluated in two groups. Those in whom MACE was observed during the long-term follow-up were considered as "MACE (+)" (n = 96) and those in whom MACE was not detected were designated as "MACE (–)" (n = 376). In our study, for the prediction of MACE and mortality and for the determination of the risk factors, MPVLR, TIMI score, and MPVLR + TIMI score combination were the parameters used. The highest cut-off values for the sensitivity and specificity values of MACE and mortality prediction for the MPVLR + TIMI score combination were determined using receiver operating characteristic curve (ROC) analysis. Study patients were evaluated in two groups, namely,"Low" and "High" MPVLR + TIMI groups, according to the MPVLR + TIMI score combination cut-off values.

Statistical analysis

The normality of the data distribution was evaluated using the Kolmogrov–Smirnov test. Numerical variables with normal distribution were expressed using mean and standard deviation. The t-test was used to compare the numerical variables between groups. For comparing the nominal data of the two groups, the χ^2 test or Fisher's exact test was used. ROC analysis was employed to calculate the predictive values of MPVLR and TIMI score as well as MPVLR + TIMI score, which is a combination of both scores, for long-term MACE and mortality. Kaplan–Meier analysis was used for long-term MACE and mortality survival analyses based on the cut-off values of MPVLR, TIMI score, and MPVLR + TIMI score. MACE-free and mortality-free survival rates of the groups were compared using the log rank test. Cox regression analysis was used to calculate the independent risk factors for the development of long-term MACE in patients who had undergone percutaneous intervention due to NSTEMI. Variables with p <0.1 in univariate analysis were evaluated using multivariate model. The relationship between the MPVLR and TIMI scores was evaluated by Pearson correlation analysis and was expressed visually through scatter plot. p-value <0.05 was considered statistically significant.

Results

The 472 NSTEMI patients evaluated in our study were categorized into two groups, namely, MACE detected (MACE (+) 96 patients) and MACE not detected (MACE (–) 376 patients) during their long-term follow-up. It was

observed that age (68.13±10.44, p <0.001], hypertension (n: 64 [66.7%], p = 0.021), diabetes mellitus (n: 44 [45.8%], p = 0.029), and chronic obstructive pulmonary disease (COPD) (n: 16 [16.7%], p <0.001) were significantly higher in the MACE (+) group than in the MACE (–) group. Although the GRACE (112±23, p <0.001) and TIMI (4.75±1.35, p <0.001) scores were significantly higher in the MACE (+) group, ejection fraction (57.56±10.81, p <0.001), lymphocyte count (5.07±1.55, p = 0.025), and GFR (92.74±18.92, p <0.001) were detected to be higher in the MACE (–) group. The demographic and laboratory data of the MACE groups are presented in Table 1.

ROC analyses of MPLVR, TIMI score, and MPVLR + TIMI score were performed for 2-year MACE and mortality prediction. For 2-year MACE prediction, it was found that MPVLR AUC = 0.864 (0.777–0.952, p <0.001), TIMI score AUC = 0.753 (0.641–0.865, p <0.001) and MPVLR + TIMI score AUC = 0.893 (0.812–0.974, p <0.001). For the two-year mortality prediction, it was found that MPVLR AUC = 0.860 (0.733–0.987, p = 0.001), TIMI score AUC = 0.642 (0.410–0.873, p = 0.210) and MPVLR + TIMI score AUC = 0.864 (0.715–1.00, p = 0.001) (Fig. 1).

Demographic and laboratory data of the "Low MPVLR + TIMI" and "High MPVLR + TIMI" groups created according to the cut-off value calculated for the 2-year MACE prediction are presented in Table 2.

Among the groups, age (66.3±10.51, p <0.001), hypertension (n: 84 [70%], p = 0.002), diabetes (n:52 [43.3%], p = 0.030), and COPD (n: 64 [13.3%], p = 0.004) rates were inferred to be significantly higher in the "High MPVLR + TIMI" group. The GRACE score (113.30±22.08, p <0.001) was found to be higher in the "High MPVLR + TIMI" group, while the ejection fraction (53.45±12.10, p = 0.032) and GFR (70.15±25.34, p <0.001] were found to be significantly lower in the same group.

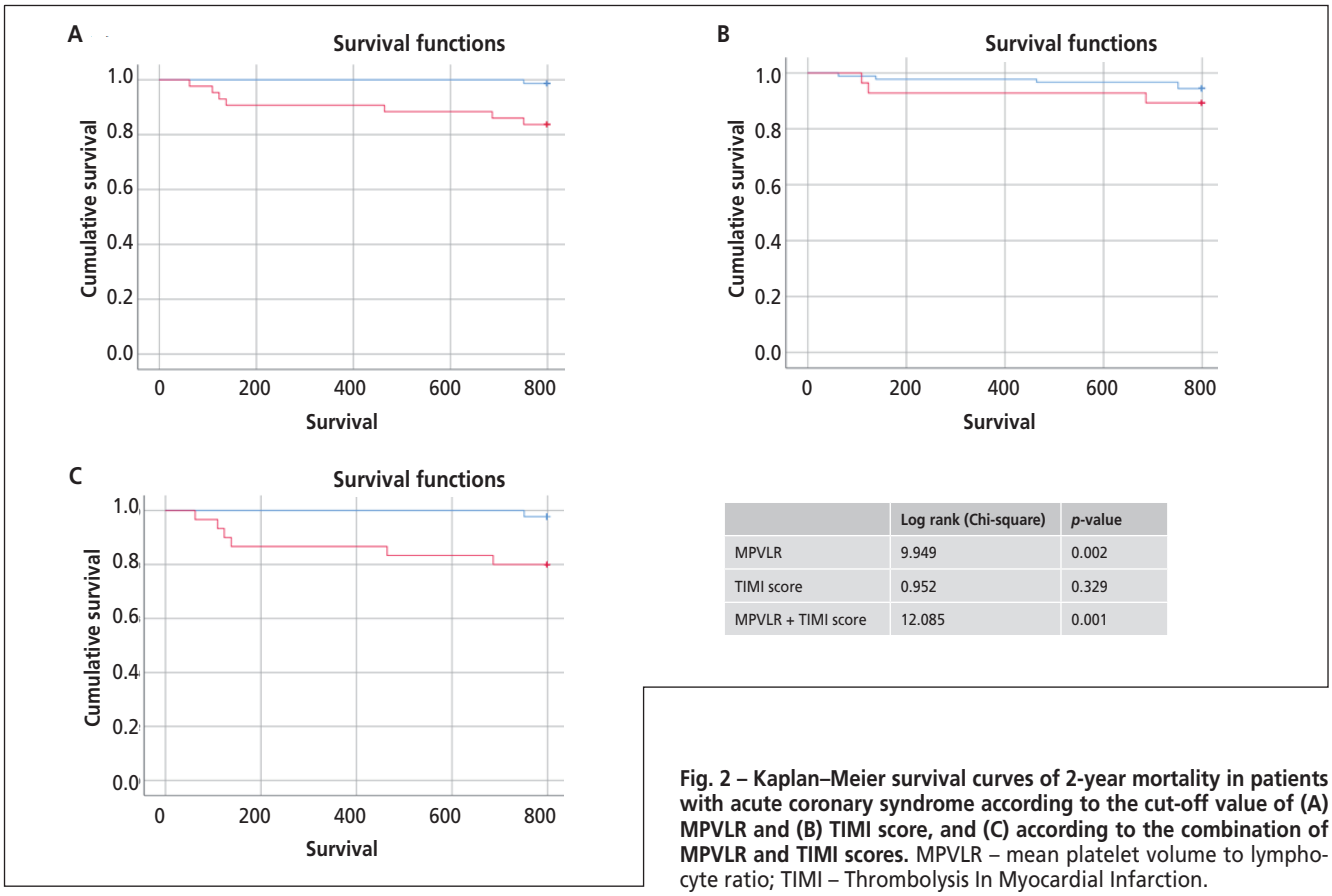
In the Kaplan–Meier survival analysis, it was noted that the MPVLR + TIMI score combination (log rank: 12.085, p = 0.001) was superior to the individual MPVLR (log rank: 9.949, p = 0.002) and TIMI score (log rank: 0.952, p = 0.329) for 2-year mortality (Fig. 2).

The MACE distributions of the "Low" and "High MPVLR + TIMI" groups are presented. In the long-term follow-up of the study patients, MACE (n: 76 [63.3%], p <0.001), mortality (n: 24 [20%], p <0.001), recurrent myocardial infarction (n: 12 [10%], p = 0.021), angina (n: 12 [10%], p = 0.021), and acute heart failure (n: 12 [10%], p = 0.021) were observed at a significantly higher rate in the "High MPVLR+TIMI" group. Adverse event distribution of the patients in the "MACE (+)" group was as follows: cardiogenic or all-cause mortality: 32, malignant arrhythmias (ventricular tachycardia, ventricular fibrillation, and grade III atrioventricular block): 8, recurrent myocardial

Table 1 – Comparison of baseline clinical characteristics of patients in the MACE (+) and MACE (–) groups

Parameters	ALL (n = 472)	MACE (+) (n = 96)	MACE (–) (n = 376)	*p*-value
Age±SD	58.08±11.13	68.13±10.44	55.51±9.8	**<0.001**
Gender (male), n (%)	368 (77.9%)	64 (66.7%)	304 (80.9%)	0.135
Hypertension, n (%)	216 (45.7%)	64 (66.7%)	152 (40.4%)	**0.021**
Diabetes mellitus, n (%)	132 (27.9%)	44 (45.8%)	88 (23.4%)	**0.029**
Current smokers, n (%)	308 (62.25%)	68 (70.8%)	240 (63.8%)	0.520
Stroke, n (%)	4 (0.84 %)	0	4 (1.1%)	0.612
COPD, n (%)	20 (4.23%)	16 (16.7%)	4 (1.1%)	**0.001**
Hyperlipidemia, n (%)	132 (27.9 %)	36 (37.5%)	96 (25.5%)	0.244
SYNTAX score±SD	15.08± 7.92	17.54±8.68	14.45±7.63	0.088
Heart rate±SD	75.17± 14.26	77.5±21.63	74.57±11.76	0.372
LVEF	57.53± 8.21	52.44±8.84	57.56±10.81	**0.001**
GRACE score±SD	98.76± 24.15	112.79±23.11	95.15±23.18	**0.001**
TIMI score±SD	3.72±1.25	4.75±1.35	3.46±1.08	**<0.001**
Lymphocyte, × 10^9/l±SD	4.40±2.43	1.78± 0.50	5.07±1.55	**0.012**
MPV, fL±SD	10.48±1.58	10.60±2.04	10.45±1.45	0.688
HGB, g/dl±SD	13.52±1.98	12.59±2.03	13.76±1.91	**0.009**
PLT, 10^3/mm^3±SD	261.48±79.95	248.58±89.48	264.78±77.51	0.378
Creatinine, mg/dl±SD	0.95±0.51	1.29±1.02	0.87±0.21	<0.001
GFR, mL/dL±SD	87.90±23.01	68.94±27.82	92.74±18.92	<0.001
MPVLR±SD	4.20±2.25	6.63±2.84	3.58±1.57	<0.001

COPD – chronic obstructive pulmonary disease; GFR – glomerular filtration rate; GRACE – Global Registry of Acute Coronary Events; HGB – hemoglobin; LVEF – left ventricular ejection fraction; MACE – major adverse cardiovascular events; MPV – mean platelet volume; MPVLR – mean platelet volume to lymphocyte ratio; PLT – platelet count; SYNTAX – SYNergy between PCI with TAXUS and Cardiac Surgery; TIMI – Thrombolysis In Myocardial Infarction.



	Log rank (Chi-square)	*p*-value
MPVLR	9.949	0.002
TIMI score	0.952	0.329
MPVLR + TIMI score	12.085	0.001

Fig. 2 – Kaplan–Meier survival curves of 2-year mortality in patients with acute coronary syndrome according to the cut-off value of (A) MPVLR and (B) TIMI score, and (C) according to the combination of MPVLR and TIMI scores. MPVLR – mean platelet volume to lymphocyte ratio; TIMI – Thrombolysis In Myocardial Infarction.

infarction: 16, recurrent angina: 16, acute heart failure: 16, and stroke: 8.

In the Kaplan–Meier survival analysis performed for 2-year MACE, it was identified that the MPVLR + TIMI score combination (log rank: 59.329, p <0.001) was superior to the individual MPVLR (log rank: 30.296, p <0.001) and TIMI score (log rank: 18.033, p <0.001).

In the regression analysis performed to determine the 2-year MACE risk factors, it was established that the MPVLR + TIMI score combination (HR: 5.41, p = 0.006) was superior to MPVLR (HR: 2.88, p = 0.094), TIMI score (HR: 2.92, p = 0.099), and other variables. Details of the regression analysis are presented in Table 3.

Specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and Pearson Chi-square analyses of MPVLR, TIMI score, and MPVLR + TIMI score combination were performed for MACE and mortality prediction (Table 4).

It was seen that the MPVL + TIMI score combination increased the specificity, PPV, and Chi-square values in predicting MACE and mortality.

Discussion

Our study aimed to generate a modified score to enhance the diagnostic power of the TIMI risk score, which has previously been proven by many clinicians to be associated with cardiovascular mortality and adverse events. For this purpose, in the combination, we preferred the MPVLR ratio that has been established to be linked to cardiovascular mortality and adverse events in the literature. In our study, we evaluated the relationship of both TIMI score and MPVLR rate with 2-year mortality and MACE and their compatibility with each other. We studied the relationship between 2-year MACE and mortality by producing combinations to accentuate the diagnostic power of both scores. We found that the MPVLR + TIMI score combination was a strong predictor of 2-year mortality and MACE when compared to individual MPVLR and TIMI scores.

In a well-designed study conducted at the cellular level by Thompson et al., it was shown that larger platelets are metabolically and enzymatically more active.[17] In the following years, clinicians found via the MPV test that the increase in platelet size also increases their activation and aggregation.[9] Platelets with increased size and metabolic activity can accelerate thrombosis and inflammatory response and adversely affect the formation and the course of ACS. As evidence for this observation, the authors have previously shown that MPV is associated with mortality and MACE in myocardial infarction patients with and without ST-segment elevation.[18,19]

The decrease in lymphocyte count is linked to an increased inflammatory response and it contributes to the growth, destabilization, and rupture of atherosclerotic

Table 2 – Comparison of baseline clinical characteristics of patients divided into groups based on MPVLR combined with GRACE scores

Parameters	ALL (n = 472)	Low MPVLR + TIMI (n = 352)	High MPVLR + TIMI (n = 120)	*p*-value
Age±SD	58.08±11.13	55.27±9.92	66.30±10.51	**<0.001**
Gender (male), n (%)	368 (77.9%)	284 (80.7%)	84 (70%)	0.223
Hypertension, n (%)	216 (45.7%)	132 (37.5%)	84 (70%)	**0.002**
Diabetes mellitus, n (%)	132 (27.9%)	80 (22.7%)	52 (43.3%)	**0.030**
Current smokers, n (%)	308 (62.25%)	228 (64.8%)	80 (66.7%)	0.851
Stroke, n (%)	4 (0.84%)	0 (0%)	4 (3.3%)	0.085
COPD, n (%)	20 (4.23%)	4 (1.1%)	16 (13.3%)	**0.004**
Hyperlipidemia, n (%)	132 (27.9%)	88 (25%)	44 (36.7%)	0.219
SYNTAX score±SD	15.08±7.92	14.31±7.74	17.33±8.14	0.071
Heart rate±SD	75.17±14.26	74.22±11.74	77.97±19.89	0.215
LVEF	57.53±8.21	56.85±9.24	53.45±12.10	**0.032**
GRACE score±SD	98.76±24.15	93.27±22.88	113.30±22.08	<0.001
TIMI score±SD	3.72±1.25	3.28±0,97	5.00±1.11	<0.001
Lymphocyte, × 10^9/L±SD	4.40±2.43	5,28±2.73	1.82±0.51	**0.010**
MPV, fL±SD	10.48±1.58	10.31±1.75	10.99±0.76	**0.044**
HGB, g/dL±SD	13.52±1.98	13.78±1.90	12.79±2.06	**0.018**
PLT, 10^3/mm^3±SD	261.48±79.95	271.36±81.74	232.50±67.68	0.021
Creatinine, mg/dL±SD	0.95±0.51	0.86±0.21	1.21±0.92	**0.001**
GFR, mL/dL±SD	87.90±23.01	93.95±18.76	70.15±25.34	<0.001
MPVLR±SD	4.20±2.25	3.38±1.50	6,60±2.36	<0.001

COPD – chronic obstructive pulmonary disease; GFR – glomerular filtration rate; GRACE – Global Registry of Acute Coronary Events; HGB – hemoglobin; LVEF – left ventricular ejection fraction; MPV – mean platelet volume; MPVLR – mean platelet volume to lymphocyte ratio; PLT – platelet count; SYNTAX – SYNergy between PCI with TAXUS and Cardiac Surgery; TIMI – Thrombolysis In Myocardial Infarction.

Table 3 – Cox regression analysis of risk factors for MACE in patients during follow-up

	Univariate			Multivariate					
				Model 1			Model 2		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.11	1.06–1.15	< 0.001	1.12	1.02–1.23	0.010	1.13	1.03–1.24	0.008
Hypertension	2.55	1.09–5.98	0.030	0.51	0.12–2.17	0.365	0.63	0.18–2.20	0.470
DM	2.33	1.04–5.20	0.039	1.88	0.60–5.89	0.277	1.33	0.45–3.98	0.600
SYNTAX score	1.05	0.99–1.10	0.058						
Hemoglobin	0.76	0.61–0.93	0.010	0.96	0.73–1.27	0.823	0.98	0.75–1.28	0.933
Creatinine	2.09	1.46–2.99	< 0.001	1.47	0.82–2.62	0.190	1.68	1.00–2.81	0.047
LVEF	0.828	0.76–0.95	< 0.001	0.893	0.78–0.98	< 0.001	0.811	0.71–0.99	< 0.001
GRACE score	1.02	1.00–1.03	0.001	0.97	0.94–1.01	0.287	0.98	0.94–1.02	0.328
TIMI score	4.84	2.16–10.84	< 0.001	2.92	0.81–10.47	0.099			
MPVLR	11.10	3.78–32.55	< 0.001	2.88	0.83–9.96	0.094			
MPVLR + TIMI	17.63	6.53–47.58	< 0.001				5.41	1.62–18.03	0.006

DM – diabetes mellitus; GRACE – Global Registry of Acute Coronary Events; LVEF – left ventricular ejection fraction; MPVLR – mean platelet volume to lymphocyte ratio; SYNTAX – SYNergy between PCI with TAXUS and Cardiac Surgery; TIMI – Thrombolysis In Myocardial Infarction.

plaques.[20] In support of this information, the lymphocyte counts of our MACE (+) patients and thosein the "High MPVLR+TIMI" group were found to be significantly lower. Calculated from the ratio of MPV to lymphocyte count, MPVLR is an easily applicable and useful parameter that provides information about thrombosis and inflammation.[16] MPVLR is an independent predictor of mortality, no-reflow, and MACE in myocardial infarction patients with

Table 4 – Specificity and sensitivity values of MPVLR, TIMI score, and MPVLR + TIMI score, combination parameters for predicting MACE and mortality

Parameters	Specificity	Sensitivity	PPV	NPV	Pearson Chi-square	*p*-value
MACE						
MPVLR	75.53	83.33	46.51	94.66	28.60	< 0.001
TIMI	84.04	54.16	46.42	87.77	15.42	< 0.001
MPVLR + TIMI	88.29	79.16	63.33	94.31	45.89	< 0.001
MORTALITY						
Parameters	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**Pearson Chi-square**	***p*-value**
MPVLR	59.09	100	15.09	100	10.52	0.001
TIMI	90.90	37.5	23.07	95.23	6.14	0.013
MPVLR + TIMI	92.72	62.5	38.46	97.14	23.20	< 0.001

MACE – major adverse cardiovascular events; MPVLR – mean platelet volume to lymphocyte ratio; NPV – negative predictive value; PPV – positive predictive value; TIMI – Thrombolysis In Myocardial Infarction.

ST-segment elevation.[21] MPVLR has also been associated with the prevalence and severity of coronary artery disease in patients with impaired coronary collateral circulation and ACS among those with stable angina pectoris.[22]

The TIMI score is an easily applicable scoring system that has been proven to be associated with mortality and cardiovascular adverse events in patients with ACS. The TIMI risk score is a useful scoring system that has been established to be linked to in-hospital and 30-day mortality and MACE in NSTEMI patients.[5,23] The TIMI score does not only predict mortality and MACE in ACS patients. In their design involving ST-elevation myocardial infarction (STEMI) patients, Halit et al. found that TIMI score predicts the prevalence of coronary artery disease when correlated with Gensini and SYNTAX scores.[24] The parameters used in the TIMI risk score are mostly composed of atherosclerotic heart disease risk factors and factors evaluating the diagnosis and severity of myocardial ischemia/infarction. The fact that thrombosis and inflammation, which are two important mechanisms in the formation and progression of atherosclerotic heart disease, are not represented by laboratory tests is an important limitation of the TIMI risk score. To overcome this disadvantage, we obtained a modified risk score by combining the TIMI risk score with MPVLR. We found that there is a significant linear correlation between MPVLR and TIMI risk scores. It was detected that MACE and mortality were encountered at higher rates in the "HighMPVLR+TIMI" group created with the cut-off value obtained for the MACE prediction of our modified score system. MPVLR + TIMI risk score combination was found to be superior to MPVLR and TIMI risk score alone in predicting long-term MACE and mortality. Moreover, it was observed that the MPVLR + TIMI risk score was superior to the diagnostic power acquired by the related scores alone in MACE-free and mortality-free survival prediction.

Examples of different designs to increase the diagnostic power of the TIMI risk score exist in the literature. In their study of 6-month MACE evaluation on 1621 NSTEMI patients, Kim et al. modified the TIMI risk score as age ≥ 65, history of coronary artery disease, Killip class ≥ 3, and NTproBNP ≥ 75th percentile, with each parameter contributing 1 point.[25] The modified TIMI score obtained with their design had a better predictive value compared to the original TIMI score for 6-month MACE in high-risk NSTEMI patients. However, it was observed that diabetes and ST-segment change were more prevalent in the MACE (+) patient group. These two factors are components of the original TIMI score. Considering that their inclusion in the modified scoring system would further increase its diagnostic power, we found it more effective to add them to the original scoring system in our model. In our study, in accordance with the previous observation, we found that age, hypertension, diabetes mellitus, and COPD rates as well as comorbidities, GRACE, and TIMI risk scores were higher in the MACE (+) group compared to the MACE (–) group. Similarly, it was observed that the ejection fraction and GFR were lower in the MACE (+) group. The parameters in question differed according to the MACE (+) group in the "High MPVLR+TIMI" group, which was created by grouping the patients according to the cut-off value obtained for the MACE prediction of the MPVLR + TIMI risk score combination. We interpreted this observation as an indicator of the compatibility of the created "High" group with the MACE (+) model. Another result supporting this compliance was that age, ejection fraction, and renal dysfunction were defined as independent risk factors for long-term MACE, and detection of these risk factors at a high rate in the "High" group supports the diagnostic power of MPVLR + TIMI score for MACE. In another design, Greenslade et al. evaluated the 30-day MACE status of 1760 patients admitted to the emergency department with chest pain using modified TIMI scores.[26] The authors obtained a modified score using four parameters of the TIMI risk score (age ≥65 years, presence of ≥3 CAD risk factors, cardiac biomarker positivity, and ECG change) and a second modified score with six parameters by adding systolic blood pressure and GFR to the four parameters. In the modified scores obtained by the researchers, ≥ 50% history of coronary artery disease, history of acetylsalicylic acid use within the last week, and ≥ 2 angina attacks within the last 24 hours increasing the susceptibility to coronary artery disease and affecting the prognosis were not included. It was shown that the mo-

dified scoring system with four parameters increased the specificity and the one with six parameters increased the sensitivity. However, there was no absolute net advantage over the original TIMI score. In our study, we found that the MPVLR + TIMI score combination obtained by adding the MPVLR ratio to the original TIMI score was superior to individual TIMI score and MPVLR in terms of specificity, PPV, and Chi-square values in predicting MACE and mortality. Moreover, we perceived that the MPVLR + TIMI risk score was a stronger independent predictor of long-term MACE than the other variables, the individual TIMI score and MPVLR.

In conclusion, the MPVLR and TIMI score combination at the time of admission has a significant predictive value for 2-year MACE and mortality after PCI in patients with ACS. Therefore, this combination can be used to identify high-risk patients with poor prognosis and to guide the treatment in the early stage of the disease. The combination of MPVLR, which is a non-invasive, simple, economic, and easily applicable parameter, with the TIMI score is a noveland beneficial diagnostic tool for the evaluation, treatment, and prognosis of patients with ACS.

Limitations

There are some limitations in our study. First, this was a single-center study with limited sample size and possible selection bias. Moreover, the prognostic value of other biomarkers in patients with ACS was not investigated. MPVLR was chosen as it was known to be better at expressing both thrombosis and inflammation. Additionally, the changes in MPVLR were not evaluated dynamically, meaning that no analysis was performed regarding the existence of a similar predictive value in MPVLR after treatment.

Conflict of interest

The authors declare that they have no competing interests.

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Ethical statement and consent to participate

The present study was approved by the Ethics Committee of Ordu University Clinical Research Ethics Committee with the ethics number of 2021/192.

Informed consent

Not applicable.

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