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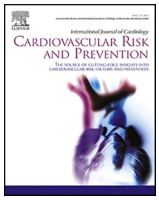

The combination of CYP2C19 polymorphism and inflammatory cell ratios in prognosis cardiac adverse events after acute coronary syndrome

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ABSTRACT

Background: *CYP2C19* gene polymorphism combination with inflammatory cell ratios was significant in the prognosis of coronary heart disease.
Materials and methods: A cross-sectional analysis study, with 6 months follow-up on 142 patients with acute coronary syndrome. Patients were analyzed for *CYP2C19* gene polymorphisms by real-time polymerase chain reaction (PCR) and complete blood count to determine inflammatory cell ratios and recorded cardiovascular events (CEs) after following up to 6 months.
Results: For 90-day CEs, *CYP2C19* gene polymorphism (Hazard Ratio (HR): 1.965, 95 % Confidence Interval (CI): 1.012–3.814), the combination of a neutrophil and lymphocyte ratio (NLR) $\geq$ 2.982 (HR: 13.001, 95 % CI: 1.37–97.304) or a platelet to lymphocyte ratio (PLR) $\geq$ 162.42 (HR: 2.878, 95 % CI: 1.212–6.835) was independent predictors of CEs. For 180-day CEs, *CYP2C19* gene polymorphism combination with NLR $\geq$3.02 (HR: 13.946, 95 % CI: 1.833–106.121) or PLR $\geq$160.38 (HR: 5.349, 95 % CI: 1.379–20.745) or monocyte to lymphocyte ratio (MLR) $\geq$ 0.3 (HR: 4.699, 95 % CI: 1.032–31.393) were independent predictors of CEs.
Conclusion: NLR, PLR or MLR combined with *CYP2C19* gene polymorphism were stronger independent predictors of cardiovascular events in patients with acute coronary syndromes compared to *CYP2C19* gene polymorphism and inflammatory cell ratios separately. *CYP2C19* polymorphism and high NLR was the strongest predictor of both CEs at 90 days and 180 days.

1. Introduction

Early prognosis and risk stratification in patients with acute coronary syndrome (ACS) increased the efficacy of diagnosis and treatment outcomes. Many classical scales have been established such as The Global Registry of Acute Coronary Events (GRACE), and Thrombolysis in Myocardial Infarction (TIMI). In addition, *CYP2C19**2, *3 gene polymorphisms, and inflammatory cell ratios were increasingly interesting in research [1–5]. Patients with *CYP2C19**2 and *CYP2C19**3 gene polymorphisms had higher levels of platelet aggregation than without them when being treated with $P2Y_{12}$ inhibitors, thereby leading to an increased incidence of cardiovascular events (CEs) after ACS [1,6,7]. A noticeable thing was that the prevalences of intermediate and poor *CYP2C19* metabolizers were significant in the world (about 40 % in the general population), especially higher in the Asian population (about 50 %) [8]. Numerous studies had shown that *CYP2C19* polymorphisms associated with an increased risk of CEs (approximately 1.99–2.88-fold) [2,5,9] after ACS. Moreover, inflammation has a vital role in the development and rupture of atherosclerosis plaque, containing the participation of peripheral blood cells, affecting their numbers in blood [10]. The neutrophil and lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume to lymphocyte ratio (MPVLR), mean platelet volumne to platelet ratio (MPVPR) had been researched in many studies and high inflammatory cell ratios resulted in worsen outcomes and poor prognosis after ACS [1,11]. Although *CYP2C19* polymorphisms and inflammatory cell ratios had been studied widely, to

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the best of our knowledge, the predictive value of CEs of the combination of them have not yet been conducted. Therefore, we performed this study to investigate the predictive value of CEs in the combination between *CYP2C19* gene polymorphism and inflammatory cell ratios in patients with acute coronary syndrome.

2. Materials and methods

2.1. Study design and population

This study aimed to examine the prognostic values for CEs of the combinations of *CYP2C19* polymorphism and inflammatory cell ratios and whether the combinations were stronger predictors than *CYP2C19* polymorphism and inflammatory cell ratios itself. We performed a cross-sectional analysis study with a 6-month follow-up on 142 patients with acute coronary syndrome from May 2021 to July 2023 at Can Tho University of Medicine and Pharmacy Hospital and Can Tho Central General Hospital. Inclusion criteria were: (1) acute coronary syndrome (ACS) including unstable angina, acute ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) according to the European Society of Cardiology 2017 and 2020 criteria [7,12]; (2) age ≥18; (3) consented to participate in the study. Exclusion criteria were: (1) Medical comorbidities that could affect survivability including malignancy, child C cirrhosis, chronic obstructive pulmonary disease (COPD) group D, and chronic kidney disease stage V (estimated glomerular filtration rate (eGFR) less than 15 ml/min/1.73 m^2 body surface area); (2) Severe bleeding; (3) Contraindications to antiplatelet therapy; (4) Hematological diseases affecting the numbers of blood cells: acute or chronic leukemia, bone marrow failure (BMF); (5) Acute/chronic infections.

After admission, *CYP2C19* polymorphism including normal metabolizer and reduced-function metabolizer (intermediate and poor metabolizer) was recorded. NLR, PLR, MLR, MPVLR and MPVPR were calculated from complete blood count (CBC). The follow-up time was 6 months for cardiovascular endpoints (all-cause death, recurrent myocardial infarction, readmission angina, ischemia stroke and heart failure).

2.2. Study contents

2.2.1. Study variables

General characteristics included age, gender, and cardiovascular risk factors such as hypertension, type 2 diabetes mellitus (T2DM), dyslipidemia, smoking, overweight and obesity (when Body mass index (BMI) ≥ 23 kg/m^2) [13], sedentary lifestyle (exercise less than 3 times a week for at least 30 min and/or no physical activity lasting ≥30 min and no sweat). Types of ACS defined as qualitative variables with 3 values (STEMI, NSTEMI, and unstable angina), diagnosed based on the European Society of Cardiology in 2017 and 2020 [7,12].

***CYP2C19* gene polymorphism characteristics** consisted of *CYP2C19* genotype classification including 2 groups: those not carrying *CYP2C19* reduced-allele (**1/*1*) and those carrying *CYP2C19* reduced-allele (genotype with *CYP2C19**2 and/or *3) and metabolic phenotypes [14].

The inflammatory cell ratios included: NLR was the number of neutrophils divided by the number of lymphocytes, PLR was the number of platelets divided by the number of lymphocytes, MLR was the number of monocytes divided by the number of lymphocytes, MPVLR was the mean volume of platelets divided by the number of lymphocytes, and MPVPR was the mean volume of platelets divided by the number of platelets.

Cardiovascular events were all-cause mortality, recurrent myocardial infarction, ischemic stroke, readmission for angina, and heart failure.

Cardiovascular events prognostic value of *CYP2C19* gene polymorphism and inflammatory cell ratios were assessed by exploring the association between gene polymorphisms, *CYP2C19* metabolizer phenotypes, inflammatory cell ratios, and cardiovascular events. Kaplan Meier event-free survival between 2 groups carrying *CYP2C19* gene polymorphisms, and inflammatory cell ratios. Univariate and multivariate Cox regression analysis assessed the predictive value of cardiovascular events in 90 days and 180 days of CEs. The Receiver Operative Characteristic (ROC) curve was used to determine the area under the curve (AUC), cut-off point, sensitivity, and specificity of inflammatory cell ratios to predict CEs at 90 days and 180 days.

2.2.2. Measurements and data collection methods

Patients enrolled in the study were examined for general information (full name, year of birth, gender, address, admission number, storage number, and contact phone number) and medical history including hypertension, dyslipidemia, smoking, sedentary, T2DM, drug using history (control hypertension, T2DM, and lipid).

CYP2C19 genotyping: 2 ml of the patients' venous blood was taken and placed in an EDTA tube. Blood samples were stored at −20 °C until being analyzed. Patients' DNA was extracted from whole blood using silica-based nucleic acid purification methods. The quality of the DNA sample was measured using a BioDrop spectrophotometer. The obtained DNA samples were analyzed for *CYP2C19* genotype at the Molecular Biology Department of Can Tho University of Medicine and Pharmacy by Real-time PCR method. The protocol was based upon the 5′ nuclease activity of Taq polymerase and using the Real Gene product set of Italy. The PCR reaction worked with primers around the mutant, as well as two fluorescent probes, one specific for the normal (wild) allele and the other for the mutant allele. The probes were attached to a fluorescent dye at the 5′ end. Fluorescence was analyzed in real-time reaction or at the endpoint, allowing the distinction of three possible genotypes (normal homozygous (wt), heterozygous, and mutation homozygous). The *CYP2C19* genotype, the *CYP2C19* metabolic phenotype, and the *CYP2C19* allele were recorded. Clinical forms of ACS were documented relaying on symptoms, electrocardiogram, and troponin kinetics. The value of NLR, PLR, MLR, MPVLR, and MPVPR were calculated based on the numbers of neutrophil, lymphocyte, monocyte, platelet, and mean platelet volume. Patients were followed-up to 6 months through telephone calls or medical examinations (Fig. 1).

2.3. Data analysis

Data were processed using Microsoft Excel and SPSS 20.0 software. Qualitative variables by calculating frequency and proportion. Quantitative variables with normal distribution were described by mean and standard deviation (SD) (mean ± SD). Quantitative variables without normally distributed were described by median and maximum–minimum values (median, maximum–minimum). ROC curve was used to determine the AUC, cut-off point, sensitivity, and specificity. The difference was statistically significant when $p < 0.05$. Use the Youden J index to determine the optimal cut-off point with the highest sensitivity and specificity. The J-index was the highest value of the sum of sensitivity and specificity minus 1: J = max (Sensitivity + Specificity – 1). Used the Kaplan-Meier estimation method to calculate the cumulative total of events at different time points. Univariate and multivariable Cox regression analysis was used to identify independent variables that affect CEs.

3. Results

3.1. General characteristic of study population

In 142 patients with acute coronary syndrome, 48.6 % of patients had *CYP2C19* gene polymorphism, in which the poor metabolizer phenotype accounted for a low rate of 6.3 %, intermediate metabolizers accounted for 42.3 %, the *CYP2C19**1 allele accounted for the highest rate (72.2 %), and the lowest was *CYP2C19**3 (7 %). The median NLR in

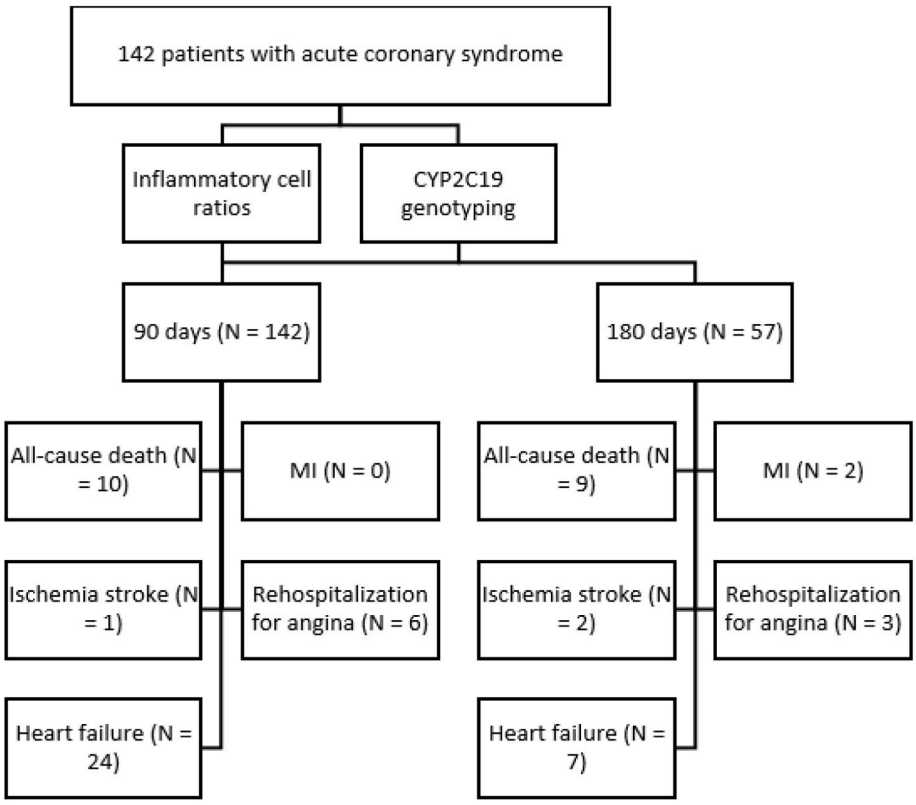

Fig. 1. Study population flow chart.

CEs group was significantly higher than that of non-CEs group, which were 4.67 (3.24–6.34) and 2.91 (1.87–5.09) respectively, p = 0.001. The other ratios did not show any significant differences between the 2 groups (p > 0.05) (Table 1).

3.2. *Predicted value of CEs of CYP2C19 polymorphisms and inflammatory cell ratios*

In 90-day follow-up (n = 142), 41 CEs (28.9 %) occurred, including 10 (7 %) all-cause deaths, 2 (1.4 %) recurrent myocardial infarctions, 2

Table 1
General characteristic of study population.

Characteristic	Overall	CEs	Non-CEs	p
Age (Mean ± SD)	67.32 ± 12.82	68.27 ± 12.49	66.9 ± 13	0.551
Male, n (%)	84 (59.2)	24 (54.5)	60 (61.2)	0.454
Hypertension, n (%)	117 (82.4)	33 (75)	84 (85.7)	0.121
T2DM, n (%)	40 (28.2)	22 (50)	18 (18.4)	**<0.001**
Dyslipimia, n (%)	59 (41.5)	31 (70.5)	35 (35.7)	**<0.001**
Smoking, n (%)	43 (30.3)	14 (31.8)	29 (29.6)	0.789
Obesity, n (%)	57 (40.1)	25 (56.8)	32 (32.7)	**0.007**
Sedentary lifestyle, n (%)	53 (37.3)	18 (40.9)	35 (35.7)	0.554
Acute coronary syndrome type:	45 (31.7)	22 (50)	23 (23.5)	**0.007**
STEMI, n (%)	83 (58.4)	19 (43.2)	64 (65.3)	
NSTEMI, n (%)	14 (9.9)	3 (6.8)	11 (11.2)	
UA, n (%)				
CYP2C19 polymorphism, n (%)	69 (48.6)	28 (63.6)	41 (41.8)	**0.016**
Metabolic phenotype	73 (51.4)	16 (36.4)	57 (58.2)	**0.032**
NM, n (%)	60 (42.3)	23 (52.3)	37 (37.8)	
IM, n (%)	9 (6.3)	5 (11.4)	4 (4.1)	
PM, n (%)				
Inflammatory cell ratios				
NLR (Median, min-max)	3.31 (0.82–33.5)	4.67 (3.24–6.34)	2.91 (1.87–5.09)	**< 0.001**
PLR (Median, min-max)	116.53 (32.13–567.5)	127.46 (95.54–199.05)	114.6 (87.85–158.06)	0.213
MLR (Median, min-max)	0.31 (0.06–2.5)	0.339 (0.25–0.487)	0.297 (0.236–0.462)	0.312
MPVLR (Median, min-max)	3.7 (0.62–16.75)	4.221 (2.958–5.75)	3.575 (2.54–5.353)	0.141
MPVPR (Median, min-max)	0.03 (0.012–0.099)	0.029 (0.023–0.047)	0.031 (0.022–0.04)	0.881
High $NLR_{90,}$ n (%)	83 (58.5)	37 (90.2)	46 (45.4)	**<0.001**
High $NLR_{180,}$ n (%)	23 (40.4)	17 (73.9)	6 (17.6)	**<0.001**
High $MPVLR_{180,}$ n (%)	27 (47.4)	16 (69.6)	11 (19.3)	**0.006**

CEs: cardiovascular events, NM: normal metabolizer, IM: intermediate metabolizer, PM: poor metabolizer, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocytes to lymphocytes ratio, MPVLR: mean platelet volume to lymphocyte ratio, MPVPR: mean platelet volume to platelet ratio, SD: standra devitation.

(1.4 %) ischemia strokes, 6 (4.2 %) readmissions for angina and 24 (16.9 %) heart failure. Only NLR had predictive value of 90-day cardiovascular events ($p < 0.001$) with an AUC of 0.713, a cut-off point of 2.982, a sensitivity of 90.2 %, and a specificity of 54.4 %. The rate of CEs in the high NLR (NLR ≥2.982) group was higher than that of the lower NLR group (NLR <2.982), the difference was statistically significant (26.1 % and 2.8 % respectively, $p < 0.001$). The group with high NLR had a lower cummulative probability of event-free survival than the group with low NLR, which was statistically significant ($p < 0.001$). Cox analysis showed that both *CYP2C19* polymorphism (HR: 1.965, 95 % CI: 1.012–3.814) and NLR ≥2.982 (HR: 6.554, 95 % CI: 2.267–18.951) were independent predictors of 90-day CEs.

In 180-day follow-up (n = 57), 23 CEs (28.9 %) occurred, including 9 (15.8 %) all-cause deaths, 2 (3.5 %) recurrent myocardial infarctions, 2 (3.5 %) ischemia strokes, 3 (5.3 %) readmissions for angina and 7 (12.3 %) heart failure. The cut-off point for NLR was 3.02 with a sensitivity of 73.9 % and a specificity of 85.4 %. The MPVLR cut-off point was 2.91 with a sensitivity of 69.6 % and a specificity of 67.6 %. The incidence of CEs in high NLR (≥3.02) group was significantly higher than in the low NLR (<3.02) group ($p < 0.001$), and in the high MPVLR group (≥2.91) was significantly higher than in the low MPVLR group (<2.91) ($p = 0.006$). The groups with high NLR and high MPVLR had lower cummulative probabilities of event-free survival than that of the group with low values, statistically significant ($p < 0.001$ and $p = 0.003$), respectively (Table 2).

3.3. The combination of CYP2C19 gene polymorphism and inflammatory cell ratios in the prognostic of cardiovascular events

Patients were divided into 2 subgroups: high–risk group: those carrying *CYP2C19* gene polymorphisms and/or high inflammatory cell ratios (defined as ≥ the cut-off values of the ROC curves) and low – risk group: those with *CYP2C19* normal metabolizer and low inflammatory cell ratios (defined as < the cut-off values of the ROC curves). The definition of high inflammatory cell ratios in 90-day CEs was NLR ≥2.982, PLR ≥162.43, MLR ≥0.3, MPVLR ≥3.06, and MPVPR ≥0.048 and in 180-day CEs prognosis was NLR ≥3.02, PLR ≥160.38, MLR ≥0.3, MPVLR ≥2.91, and MPVPR ≥0.025. The proportion of patients with CEs was higher in high-risk group, significantly for the *CYP2C19* gene polymorphism associated with NLR, PLR, MLR at 90 days, and the incidence of CEs in the group with the polymorphism and/or high NLR, PLR, MLR was higher than that of the group without the gene polymorphism and low ratios ($p < 0.05$) at 180 days time point. The probability of CEs-free survival was significantly lower in patients with *CYP2C19* gene polymorphism and/or high NLR ($p < 0.001$). The probability of CEs-free survival was lower in: Patients with *CYP2C19* gene polymorphism and/or high PLR ($p = 0.015$ and $p = 0.01$) or patients with *CYP2C19* gene polymorphisms and/or high MLR ($p = 0.006$ and $p = 0.018$) (Table 2).

In 90 days, Cox analysis showed that *CYP2C19* polymorphism (HR: 1.965, 95 % CI: 1.012–3.814), NLR ≥2.982 (HR: 6.554, 95 % CI: 2.267–18.951), the combination of *CYP2C19* gene polymorphism and NLR (HR: 13.001, 95 % CI: 1.37–97.304, $p = 0.013$) or PLR (HR: 2.878, 95 % CI: 1.212–6.835) were independent factors for CEs. Regarding CEs at 180 days, independent prognostic factors for the CEs included: NLR ≥3.02 (HR: 7.893, 95 % CI: 2.892–21.25, $p < 0.001$), MPVLR ≥2.91 (HR: 3.397, 95 % CI: 1.361–5,478, $p = 0.009$), high – risk group of the combination of *CYP2C19* gene polymorphism and NLR (HR: 13.946, 95 % CI: 1.833–106.121, $p = 0.011$), or PLR (HR: 5.349, 95 % CI: 1.379–20,745, $p = 0.015$) or high MLR (HR: 4.699, 95 % CI: 1.032–31.393, $p = 0.045$). The HRs of combination of *CYP2C19* polymorphism and NLR were the highest among independent risk factors in both 90-day and 180-day CEs. In 90-day follow-up, although PLR had not a significantly predictive value for CEs, the risk of CEs increased 2.878-fold (95 % CI: 1.212–6.835) after combining PLR and *CYP2C19* polymorphism. Similarly, in 180-day follow-up, PLR and MLR individually were not predictive factors for CEs but when combinating them with *CYP2C19* polymorphism, it showed that the combinations were all significantly independent risk factors for CEs and their HRs were both higher than that of *CYP2C19* polymorphism. (Table 2), (Fig. 2).

4. Discussion

In this study, we found that *CYP2C19* polymorphism, NLR ≥2.982, the combination of *CYP2C19* polymorphism and high NLR or high PLR were independent predictors for 90-day CEs. The combinations *CYP2C19* polymorphism – high NLR and *CYP2C19* polymorphism – high PLR had better performances in prognostic CEs after ACS compared to *CYP2C19* polymorphism, NLR and PLR separately. In 180 days, independent predictors for CEs were high MPVLR, the cominations of *CYP2C19* polymorphism and NLR/PLR/MLR. High MPVLR was an independent predictor, yet, when we combined it with *CYP2C19* polymorphism, the combination fell to be a strong predictor for CEs. In contrast, the combination between *CYP2C19* polymorphism and NLR, PLR and MLR increased the predictive value of CYP2*C19* polymorphism and these ratios after ACS.

There is a large quantity of studies about prognostic value of *CYP2C19* polymorphism and inflammatory cell ratios solely. Zhisong Wang and Juan Wang's study in 2020 demonstrated the prognostic value of NLR: AUC 0.72 (95 % CI: 0.625–0.814), cut-off point was 2.918, sensitivity and specificity was 68.8 % and 77 %, respectively. NLR was associated with CEs after 1 year of follow-up (OR: 1.307, 95 % CI: 1.034–1.651, p = 0.025) [11]. A systematic review of 8932 ACS patients found that PLR >150 was a prognostic factor for both long-term and

Table 2
Cox regression examined prognostic factors for cardiovascular events at 90 days and 180 days.

Variables	CEs within 90 days (n = 142)				CEs within 180 days (n = 57)			
	Univariate		Multivariable		Univariate		Multivariable	
	HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p
High NLR	8.392 (2.986–23.581)	<0.001	6.554 (2.267–18.951)	**0.001**	7.881 (3.06–20.293)	**<0.001**	7.893 (2.892–21.25)	**<0.001**
CYP2C19	1992 (1055–3763)	0,034	1965 (1012–3814)	**0,046**	2145 (0,881–5,22)	0,093	2234 (0,862–5789)	0,098
CYP2C19 and/or high NLR	16.502 (2.267–120.104)	0.006	13.001 (1.37–97.304)	**0.013**	14.461 (1.945–107.527)	0.009	13.946 (1.833–106.121)	**0.011**
CYP2C19 and/or high PLR	2.943 (1.303–6.645)	0.009	2.878 (1.212–6.835)	**0.017**	4.256 (1.262–14.351)	0.02	5.349 (1.379–20.745)	**0.015**
CYP2C19 and/or high MLR	2.423 (1.019–5.762)	0.045	2.24 (0.919–5.463)	0.076	4.777 (1.119–20.4)	0.035	4.699 (1.032–31.393)	**0.045**
CYP2C19 and/or high MPVLR	1.511 (0.593–3.853)	0.387			2.864 (0.85–9.649)	0.09		
CYP2C19 and/or high MPVPR	1172 (0,898–3265)	0.103			2864 (0,85–9649)	0,09		

CEs: cardiovascular events, CI: confidence intervals, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocytes to lymphocytes ratio, MPVLR: mean platelet volume to lymphocyte ratio, MPVPR: mean platelet volume to platelet ratio, HR: Hazard ratio.

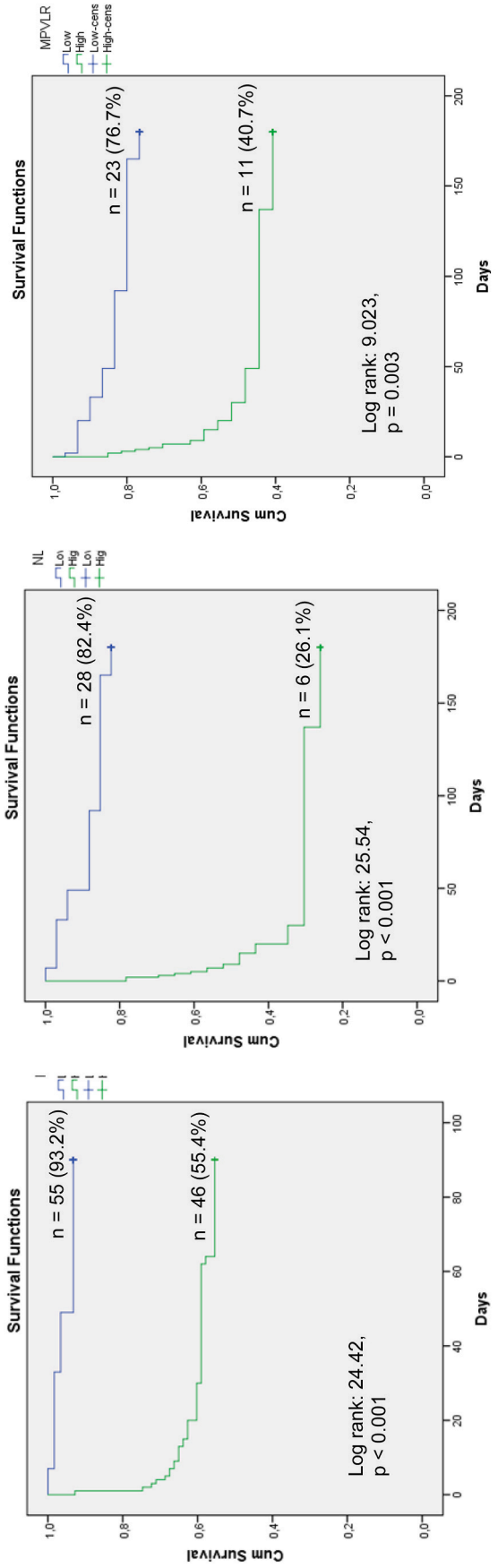

Fig. 2. The Kaplan Meier plot showed cumulative event-free survival by NLR subgroups at 90 days (A) and NLR, MPVLR at 180 days (B).

in-hospital CEs [3]. In another study by Xinsen Chen (2020) on 1009 STEMI, MPVLR was an independent predictor of 90-day mortality (HR: 1.430, 95 % CI: 1.287–1.643, $p < 0.001$) [4]. Currently, there were very few studies related to MPVPR and CEs, similar to our study, the study of Ismail Bolat et al. (2015): High MPVPR was associated with recurrent MI after 1 year, but not with in-hospital mortality within 1-month and 1-year followed-up in STEMI patients with PCI [5]. Nevertheless, according to our knowledge, the prognostic value of the combinations of *CYP2C19* polymorphism and inflammatory cell ratios in ACS patients have not yet been researched.

The mechanisms for our main findings remain unclear. It could be due to the concomitant effect of the *CYP2C19* gene polymorphism and inflammatory response on hepatic cytochrome *CYP2C19* enzyme activity. A meta-analysis by Milo Gatti and Federico Pea of 26 studies found that an inflammatory response decreased *CYP2C19* enzyme activity (as demonstrated by a 1.29–1.97-fold dropping in omeprazole clearance) [15]. Another study was conducted to investigate the effect of inflammation (via a tablet marker, CRP index) on cytochrome P450 activity in the liver. The study found a 57 % decrease in *CYP2C19* activity ($p = 0.0002$) in acute inflammation and biomarkers for inflammatory response (CRP) were negatively correlated with significant *CYP2C19* enzyme activity ($r = - 0.417$, $p = 0.0001$) [16]. The 2021 study reported the effect of an inflammatory response that reduced the effect of cytochrome *CYP2C19*. Specifically, in patients with *CYP2C19* poor metabolizer (*2/*2, *2/*3), the cytochrome *CYP2C19* activity declined by an inflammatory respone decreased more than that of NM phenotype (*1/*1) [17]. As a result, patients with 2 associated factors such as *CYP2C19* gene polymorphism and high inflammatory activities could led to reducing in *CYP2C19* enzyme activity, further reducing the inhibitory effect on platelet aggregation of P2Y12 inhibitors and worsening treatment outcomes. In clinical practice, physicians need to acknowledge that patients presented with *CYP2C19* polymorphism and/or high inflammatory have increased incidence of CEs and should be considered as high-risk patients and received more aggressive treatment such as early PCI.

Our study had some limitations. Firstly, we did not perform platelet aggregation tests, hence, the comparison between platelet aggregation of low-risk group and high-risk group could not be analyzed to gain a better explanation for our findings. Secondly, our sample size was relatively small, and the follow-up time was quite short, so further large studies may need to be established.

5. Conclusion

According to the results, the combination of *CYP2C19* gene polymorphisms and NLR or PLR were independent factors for 90-day CEs, whereas *CYP2C19* gene polymorphism combined with NLR, PLR or MLR were significantly increased rate of 180-day CEs and the combinations had better performances in prognostic CEs compared to that of each individual. The combination *CYP2C19* polymorphism and high NLR was the strongest predictor in both 90-day and 180-day CEs.

Author contribution

Conceptualization; Nha Tran Khuong Nguyen, An Viet Tran. Methodology; Toan Hoang Ngo, Nha Tran Khuong Nguyen. Software; Nha Tran Khuong Nguyen, Toan Hoang Ngo. formal analysis; Nha Tran Khuong Nguyen, An Viet Tran. data curation; Nga Ngoc Thi Pham, Nha Tran Khuong Nguyen. writing original draft preparation; Toan Hoang Ngo, An Tuan Huynh, Khue Duy Nguyen. writing review and editing; Toan Hoang Ngo, Nha Tran Khuong Nguyen, Nga Ngoc Thi Pham, Bao Lam Thai Tran, An Tuan Huynh, Khue Duy Nguyen, Khuong Duy Nguyen, An Viet Tran. All authors have read and agreed to the published version of the manuscript.

Ethics approval

Our study was approved by the Institutional review board of Can Tho University of Medicine and Pharmacy (Approval number: 188/PCT-HDDD, 31/03/2021).

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Conflict of interest

None to declare.

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Appendix. Kaplan Meier chart showing cumulative event-free probability

List of abbreviations

AUC	Area under the curve
CYP2C19	Cytochrome P450 2C19
IM	Intermediate Metabolizers
LDL – c	Low Density Lipoprotein Cholesterol
MLR	Monocyte to lymphocyte ratio
MPVLR	Mean platelet volume to lymphocyte ratio
MPVPR	Mean platelet volume to platelet ratio
NLR	Neutrophil to lymphocyte ratio
NM	Normal Metabolizers
PCI	Percutaneous Coronary Intervention
PCR	Polymerase Chain Reaction
PLR	Platelet to lymphocyte ratio
PM	Poor Metabolizers
ROC	Receiver operating characteristic

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