Factors Associated with 30-day Major Adverse Cardiovascular Event in Acute Coronary Syndrome Patients with Non-Dialysis Chronic Kidney Disease: A Retrospective Cohort Study

Eka Ginanjar[1], Ni Made Hustrini[2], Arif Mansjoer[1], M. Shiddiq Al Hanif[3]*

[1]Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

[2]Division of Nephrology-Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

[3]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Eka Ginanjar, MD., PhD. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo General Hospital. Jl. Diponegoro 71, Jakarta 10430, Indonesia. Email: ekaginanjar.MD@gmail.com.

ABSTRACT

Background*: Acute coronary syndrome (ACS) accounts for the majority of ischemic heart disease-related deaths. It is known that ACS patients with chronic kidney disease (CKD) tend to have worse clinical outcomes, including major adverse coronary events (MACE) compared to patients without CKD. Some studies suggested that several determinant factors may be involved in this condition. Until now, research on determinant factors of MACE in ACS patients with CKD in Indonesia is still limited. Thus, we aimed to investigate the relationship of various factors to MACE in ACS patients with non-dialysis CKD who underwent percutaneous coronary intervention (PCI), in the form of neutrophile leukocyte ratio (NLR) as a factor describing chronic inflammation, left ventricular hypertrophy (LVH) as a factor describing cardiac remodeling, Gensini score may represent coronary severity, whereas GRACE was used to evaluate the severity and clinical risk of ACS patients.* ***Methods:*** *This study is a retrospective cohort study using secondary data from the medical records of 117 ACS patients who underwent percutaneous coronary intervention (PCI) at Cipto Mangunkusumo General Hospital Jakarta from January 2018 to June 2018 . Patients were classified based on the stage of CKD and assessed for 30-day MACE. Data were recorded on GRACE score, Gensini score, LVH, and neutrophil-lymphocyte ratio (NLR). Analysis of the relationship between these factors was carried out using the chi-square test.* ***Results****: Of the 117 patients, 62.3% were STEMI. At the end of hospital treatment, 67.5% were in the normal-stage 2 CKD group, 17.1% in the CKD stage 3a-3b group, and 15.4% in the CKD stage 4-5 group. MACE occurred in 47 (40.2%) patients with 17 (14.5%) dying. There was a significant relationship between GRACE scores and MACE (54.8% MACE at high GRACE scores vs. 32% MACE at low-moderate GRACE scores, p = 0.016, OR: 2,57 CI 95%, 1,18-5,59), while no significant relationship was found for the Gensini score, LVH, and NLR scores even though there was an increase in the proportion of MACE.* ***Conclusion:*** *The incidence of MACE is higher than in the previous studies conducted in the same place, i.e. Cipto Mangunkusumo General Hospital, no significant relationship is found in NLR, LVH, and Gensini score with the 30-day MACE of ACS patients with non-dialysis CKD, meanwhile the GRACE score correlates with the 30-day MACE of ACS in non-dialysis CKD patients as is the known theory regarding this score.*

Keywords*: ACS, CKD, MACE, GRACE score, Gensini score, LVH, NLR.*

INTRODUCTION

Acute coronary syndrome (ACS) and sudden death account for the majority of ischemic heart disease-related deaths with at least 1.8 million deaths caused by ACS every year.[1] The American Heart Association (AHA) estimates that one person has a heart attack every 41 seconds.[2] In Indonesia, cases of heart disease reached 1,017,290 with a mortality percentage of 35% of the total.[3] Similar to ACS, the prevalence of chronic kidney disease (CKD) increases and causes global health problems.[4] It is reported that 14.9% of the adult population in the United States in 2015-2018 suffered from CKD. In Indonesia, there are 132.142 patients with CKD undergoing hemodialysis in 2018.[5]

Several studies are showing an association between ACS and CKD. A study found that the risk of ACS increased linearly, and patients with CKD stages 3a to 4 had a 2-3 times chance of cardiovascular mortality compared to patients without CKD.[6] Major Adverse Cardiovascular Event (MACE), a term used to describe important poor clinical outcomes in ACS patients[7], showed an increased by one year post percutaneous coronary intervention (PCI) in CKD patients compared to ACS patients with normal renal function.[8] Another study also showed that during follow-up, patients with severe renal dysfunction were an independent risk factor for MACE, and were associated with poor prognosis.[9]

Experts have investigated the relationship between ACS and CKD through the determinant factors involved in MACE. A study found that the chronic inflammatory process through increased chemotactic activity, tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6) in the arteries of CKD patients resulted in endothelial damage to blood vessels, thereby accelerating the process of atherosclerosis.[10,11] This finding is also supported by other studies that prove that patients with CKD stage 1-4 with a high neutrophil-lymphocyte ratio (NLR) have a worse outcome than patients with low NLR.[11] In addition, the high prevalence of congestive heart failure in CKD patients is associated with cardiac remodeling to the occurrence of left ventricular hypertrophy (LVH). A population study based on autopsy data found that lower glomerular filtration rate (GFR) was associated with greater left ventricular wall thickness,[12] whereas in the 4D study, the presence of LVH was associated with a nearly doubled risk of sudden cardiac death in CKD patients.[13]

As a method that attempts to quantify the overall coronary atherosclerosis burden[14], it was found that the Gensini score in CKD patients was higher.[8] Similar to this finding, CKD patients also have worse coronary artery stenosis and higher three-vessel disease incidence compared to patients with normal kidney function and CVD problems.[8] This condition may occur due to several mechanisms, including microinflammation, oxidative stress, endothelial dysfunction, impaired lipid metabolism, uremic toxins such as homocysteine, glycation end products, protein oxidation end products, parathyroid adenine, abnormal calcium, and phosphorus metabolism, asymmetric dimethylarginine, hyperuricemia, and other factors that can cause damage to the vascular endothelium thereby increasing the occurrence of chronic renal insufficiency, activation of the renin-angiotensin-aldosterone system and hypertension.[8,15,16] Additionally, the researchers observed that CKD shared both traditional (such as hypertension, diabetes, and dyslipidemia) and non-traditional (such as homocysteinemia, calcium and phosphate disorders, elevated serum uric acid levels, C-reactive protein, and other oxidative stress as well as inflammatory markers levels) risk factors that have multiple or superimposed effects on atherosclerosis and vascular endothelial damage.[8,16,17]

To date, research on determinant factors of MACE in ACS patients with CKD in Indonesia is still limited. Thus, this study aimed to analyze the role of 30-day MACE factors in ACS with non-dialysis CKD patients by assessing its determinants including NLR, LVH, Gensini score, and GRACE score.

METHODS

The study was a retrospective cohort study performed at Cipto Mangunkusumo General Hospital Jakarta as the national referral hospital in Indonesia.

Study Population

This study analyzed secondary data from the study entitled "Effect of Beta2-Microglobulin and Fibroblast Growth Factor 23 on Coronary Severity and Major Adverse Cardiac Events in Patients with Acute Coronary Syndrome Having Chronic Kidney Disease".[18] Patients undergoing treatment at the intensive cardiac care unit (ICCU) Cipto Mangunkusumo General Hospital Jakarta with a diagnosis of ACS and coronary angiography conducted between January 2018 and June 2018 were considered for this study. All adult patients (> 18 years old) admitted to the hospital, diagnosed with ACS with non-dialysis CKD, undergoing coronary angiography, and hospitalized in Cipto Mangunkusumo General Hospital between January 2018 and June 2018, including patients with CKD stage 5 who did not undergo dialysis procedure were eligible for inclusion. Exclusion criteria were CKD patients undergoing hemodialysis, and patients with severe comorbidities, including acute stroke, hepatic cirrhosis, chronic inflammatory disease, sepsis, autoimmune, and malignancy. Pregnant women and breastfeeding mothers were excluded from this study. Incomplete medical record data such as incomplete variable data were also excluded.

Data Collection

Data for this study were collected using consecutive sampling methods collected from the previous study data that was taken from the ICCU and internal medicine ward at Cipto Mangunkusumo General Hospital. Case definitions were based on clinical diagnosis. The diagnosis of ACS was based on clinical symptoms, electrocardiogram, echocardiography, and elevated cardiac enzymes.[2,19] The diagnosis of CKD was established previously based on the serial examination of creatinine serum. The first examination is at the time of admission and the next examination is at the time the patient is discharged from the hospital. This examination was conducted to distinguish between CKD and acute kidney injury due to cardiorenal-related conditions. Additionally, we also defined CKD by the elevation of creatinine serum, decreased estimated GFR, and evidence of kidney damage (albuminuria).[20] The non-dialysis CKD was defined as patients with CKD who did not undergo dialysis procedures. GRACE score and NLR were calculated based on clinical condition and laboratory data during admission and the Gensini score was calculated based on the result of coronary angiography during hospitalization. LVH was calculated based on echocardiography during hospitalization. Patients were followed from admission to 30 days after hospitalization to determine MACE.

Data Analysis

Identified data were further analyzed with STATA. Each variable was analyzed to determine the distribution and percentage. Furthermore, categorical data were presented in the table and numerical data in mean (SD) or median (IQR) depending on the data distribution. The bivariate analysis was carried out to find out the association between the independent variables (NLR, LVH, GRACE score, and Gensini score) with the dependent variable (30-day MACE) using the chi-square test.

Ethical Approval

This study was approved by the institutional review board of the Faculty of Medicine Universitas, Indonesia with the number KET-110/UN2.F1/ETIK/PPM.00.02/2021. The consent was waived by the ethics committee due to the negligible risk nature of data collection by retrospective datasets already on electronic health records.

RESULTS

117 samples from previous studies were included (**Figure 1**). The characteristics of the patients are shown in **Table 1**. The proportion of men was 77.8% with the mean age of the patient being 57.79 years. The most common risk factors were hypertension, smoking, and diabetes mellitus, respectively. The median NLR was 4.83 with the lowest value of 1.25 and the highest value of 29.63. To determine the NLR cut-off, a receiving operating curve (ROC) analysis was performed on MACE, and the cut-off was determined to be 4.8. The median GRACE score was 110 with 64.1% of patients having a category score ≤ 128. The results of echocardiography showed that 53.1% of the subjects had LVH

with the predominantly eccentric type (73.3%). Coronary angiography found that 65.8% had multivessel disease with a median Gensini score of 50. At the end of hospitalization, the mean eGFR was 68.5 mL/min/1.73m^2 with a median of creatinine 1.1 mg/dL, with the lowest value of 0.5 mg/dL and the highest value of 11.5 mg/dL. Based on the stage of CKD, the highest proportion was found in stage 2 (37.6%), subjects who had eGFR less than 60 ml/min/1.73m^2 38 (32.5%). To simplify the analysis, we divide CKD categories into stages 1-2, 3a-3b, and 4-5 with the highest proportion found in stages 1-2 (67.5%). After 30 days of follow-up, MACE occurred in 47 patients (40.2%) (**Table 2**).

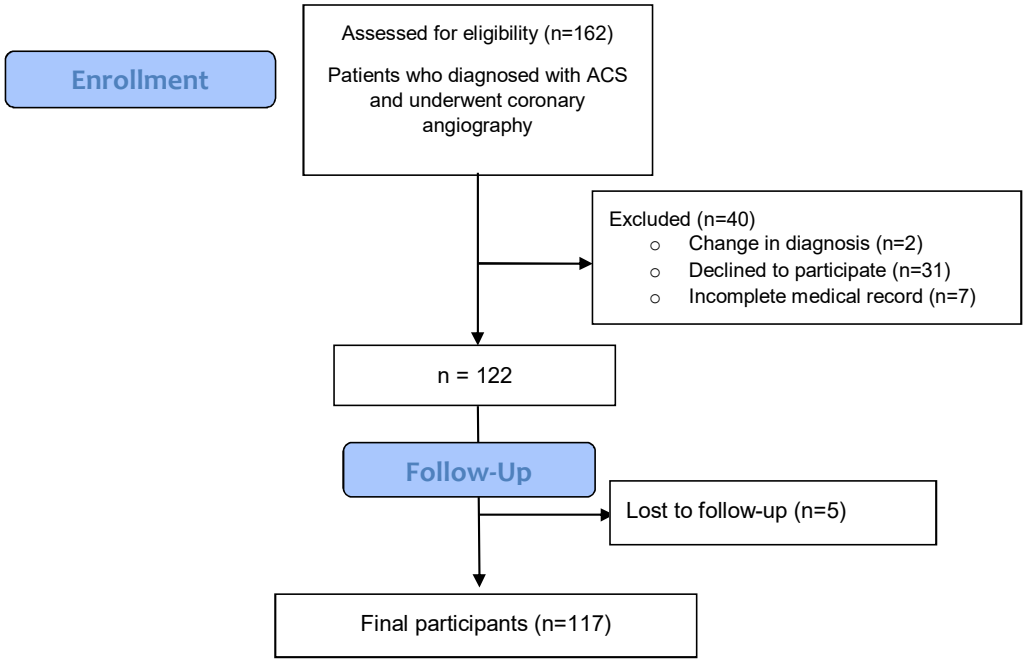

Figure 1. Flowchart of sample selection.

Table 1. Characteristics of the patients.

Characteristic	All Subject	MACE	
	(n=117)	Yes (%)	No (%)
Gender, n (%)			
Men	91 (77.8)	39 (42.9)	52 (57.1)
Women	26 (22.2)	8 (30.8)	18 (69.2)
Age, mean (SD), years	57.8 (10)		
Risk Factor, n (%)			
Diabetes mellitus	46 (39.3)	16 (34.8)	30 (65.2)
Dyslipidemia	35 (29.9)	12 (34.3)	23 (65.7)
Hypertension	76 (65)	34 (44.7)	42 (55.3)
Obesity	15 (12.8)	8 (53.3)	7 (46.7)
Chronic kidney disease (anamnesis)	8 (6.8)	3 (37.5)	5 (62.5)
Cigarette smoking	73 (62.4)	29 (39.7)	44 (60.3)
Family history CHD, n (%)	4 (3.4)	1 (25)	3 (75)
NLR, median (min-max)	4.83 (1.25-29.63)		
NLR Classification, n (%)			
NLR < 4.8	51 (49)	20 (39)	31 (61)
NLR ≥ 4.8	53 (51)	24 (45)	29 (55)

Diagnosis ACS, n (%)			
STEMI	73 (62.3)	25 (34.2)	48 (65.8)
NSTEMI	21 (18)	9 (42.9)	12 (57.1)
UAP	23 (19.7)	12 (54.5)	10 (45.5)
GRACE score, mean (SD)	119 (40.8)		
GRACE score classification, n (%)			
Low-Medium (≤128)	75 (64.1)	24 (32)	51 (68)
High (> 128)	42 (35.9)	23 (54.8)	19 (45.2)
Systolic function, n (%)			
Normal, ≥ 50%	63 (55.8)	20 (32.3)	42 (67.7)
Decrease	53 (46.9)	24 (47.1)	27 (52.9)
LVH, n (%)			
Yes, IVS or LVPW > 12 mm	60 (53.1)	26 (43.3)	34 (56.7)
No	53 (46.9)	18 (34)	35 (66)
Gensini score, median (min-max)	50 (0-132)		
Gensini score classification Gensini score, n (%)			
Low < 18	17 (14.5)	6 (35.3)	11 (64.7)
Medium 18-41	33 (28.2)	14 (42.4)	19 (57.6)
High > 41	67(57.3)	27 (40.3)	40 (59.7)
Vessel Disease, n (%)			
0	6 (5.1)	2 (33.3)	4 (66.7)
1	34 (29.1)	15 (42.9)	20 (57.1)
2	34 (29.1)	11 (31.4)	24 (68.6)
3	35 (29.9)	19 (46.3)	22 (53.7)
Left Main Disease	8 (6.8)	5 (62.5)	3 (37.5)
GFR, mL/min/1.73m^2, mean (SD)	68.57 (29.78)		
Creatinine, median (min-max)	1.1 (0.5 – 11.5)		
CKD stage, n (%)			
1	35 (30)	11 (31.4)	24 (68.6)
2	44 (37.6)	15 (34.1)	29 (65.9)
3a	13 (11.1)	5 (38.5)	8 (61.5)
3b	7 (6)	5 (71.4)	2 (26.8)
4	8 (6.8)	5 (62.5)	3 (37.5)
5	10 (8.5)	6 (60)	4 (40)
CKD stage, n (%)			
Stage 1 – 2	79 (67.5)	26 (33)	53 (67)
Stage 3a – 3b	20 (17.1)	10 (50)	10 (50)
Stage 4 – 5	18 (15.4)	11 (61)	7 (39)

Table 2. Characteristics of MACE.

Characteristics of MACE	Incidence (n=117) n (%)
MACE	
Yes	47 (40.2)
Mortality	17 (14.5)
Stroke	6 (5.1)
Cardiogenic shock	6 (5.1)
Heart Failure	34 (29)
Arrhythmia	9 (7.7)
Recurrent miokardial infarction	17 (14.5)
Time to Event	
1 day	23 (48.9)
2 day	4 (8.5)
3 day	5 (10.6)
4 day	4 (8.5)
5 day	2 (4.3)
10 – 20 day	4 (8.5)
21 – 30 day	5 (10.6)
No	70 (59.8)

Bivariate analysis results showed that there was a significant relationship between the GRACE score and MACE (54.8% MACE at high GRACE score vs. 32% MACE at GRACE score low-medium, p = 0.016, OR: 2,57 CI 95%: 1,18-5,59), while no statistically significant relationship was found with the Gensini, LVH, and NLR scores even though an increase in the number of MACE along with an increase in the degree of the Gensini score (6,14, and 27), more MACE in LVH (43.3%) than without LVH (34%), and a higher proportion of MACE in NLR 4.5 than MACE at NLR < 4.8 (45% vs. 39%) was observed (**Table 3**).

Table 3. Bivariate analysis for MACE.

Independent Variables	MACE (n=117)	
	OR (CI 95%)	P value
GRACE score	2.57 (1.18-5.59)	0.016
Gensini score	-	0.888
LVH	1.48 (0.69-3.19)	0.308
NLR	1.283 (0.588-2.799)	0.531

DISCUSSION

This study was a retrospective cohort study of ACS patients with non-dialysis CKD who underwent coronary angiography between January 2018 to June 2018 in Cipto Mangunkusumo General Hospital. The findings of this study showed that the incidence of MACE was 40.2%. It was higher than the incidence of MACE from previous studies at Cipto Mangunkusumo General Hospital in 2013 (14%) and 2016 (19.2%).[21,22] This increased incidence of MACE may be related to the characteristics of patients who were diagnosis specifically with non-dialysis CKD and it is also influenced by the tiered referral system in Indonesia which makes patients come with more severe conditions to Cipto Mangunkusumo General Hospital because this hospital is a national referral hospital.

Another finding in this study was the patients with MACE at NLR ≥ 4.5 showed no statistically significant compared to MACE at NLR < 4.8 (45% vs. 39%, p = 0.531). This may be due to the amount and distribution of data and NLR data collection. The NLR data was taken when the patient was admitted to the hospital or in the initial condition of the ACS attack, the ACS condition itself is a condition of physical stress that will trigger an increase in inflammation, which can affect the picture of chronic inflammation as a baseline for CKD patients. However, a previous study found that ACS patients with a high NLR value > 4.5 had higher mortality compared to ACS patients with NLR < 1.5.[23] Another study reported that there was a significant difference in ACS patients with NLR > 6.52 compared to NLR < 3.4 for 1 year-MACE, 1 year-mortality, in-hospital MACE, and in-hospital mortality.[24]

We also found that the condition of LVH was reported in 53.1% of patients dominated by the eccentric type (73.3%) and 46.9% of patients experienced a decrease in systolic function with a median ejection fraction of 54%. Several studies have found that CKD is associated with cardiac remodeling, which is mostly manifested by LVH and increased fibrosis.[25] LVH was also observed to be more common in individuals who started renal replacement therapy and dialysis procedure.[26] Meanwhile, some recent studies indicated that LVH begins to occur in the early stage of CKD patients.[13] The prevalence of LVH in individuals with GFR > 30 mL/min/1.73 m^2, before starting renal replacement therapy, and after starting dialysis was 16-31%, 60-75%, and 90%, respectively.[27] As a result of LVH, myocardial apoptosis, and intermyocardial fibrosis, decreased myocardial capillary density concomitantly with diastolic and systolic dysfunction, impaired intraventricular conduction, and dilatation of cardiac chambers occur. Then progressively, compensatory hypertrophy, dilatation, and cardiac dysfunction (uremic cardiomyopathy) also occurs.[28] The severity and persistence of LVH are strongly associated with the risk of death and cardiovascular events in CKD patients. Several studies revealed that a 10% reduction in LV mass was associated with a 28% reduced risk of cardiovascular death in the group of patients undergoing hemodialysis.[29,30] Whereas in the 4D study, the presence of LVH was associated with twice the risk of sudden cardiac death.[31]

The median Gensini score was found of 50, with a minimum value range of 0 and a maximum value range of 132, and 57.3% of the individuals fell into the high Gensini score category. Several studies have linked an increase in the Gensini score with an increase in the stage of CKD. For example, a study found that patients with CKD stage 5 had the highest Gensini score and that there was a significant difference in patients with normal renal function to CKD stage 2 vs. CKD stage 3, CKD stage 3 vs. CKD stage 4, and in CKD stage 4 vs. CKD stage 5.[15] Despite an increase in the number of MACE with increased Gensini scores, no significant association was found in this study's analysis of the relationship between Gensini scores and 30-day MACE. However, a previous study discovered a significant difference in the mean Gensini scores of survivors and patients who died in hospital in the study of the

association between Gensini scores and mortality in STEMI patients in Turkey.[32] In China, a study found that there was a significant correlation between Gensini scores and all one-year causes of death in patients with myocardial infarction with a mean Gensini score higher in patients who experienced death compared to survivors.[33] However, both studies merely investigate the death as an outcome and did not look in detail at how it relates to impaired renal function.

Moreover, the median GRACE score was 110 with 45.3% of subjects in the moderate GRACE score category and 35.9% in the severe category. Based on the stage of CKD, the highest proportion was found in stage 2 (37.6%), followed by stage 3 (17.1%), while patients with GFR < 60 mL/min/1.73m^2 were 32.5%. A significant correlation was found between the stage of CKD and the degree of GRACE score ($p = 0.002$). It was also revealed that CKD stage 4-5 obtained more than a large proportion of high GRACE scores compared to low-medium GRACE scores (66.7% vs. 33.3%) and this finding was not found in the CKD stage 1-2 (25.3% vs. 74.7%). Aside from creatinine levels, CKD may be linked to an increase in the value of other assessed variables in the GRACE score. A previous study conducted using GRACE found that patients with moderate or severe renal impairment have older age-related features and had more comorbidities than patients with normal or mildly impaired renal function.[34] It was also found that patients with impaired and severe renal function are twice and four times as likely to die compared to normal and mildly impaired renal function, respectively.[34] This is consistent with the findings of this investigation. Another study found that the GRACE score in patients with end-stage renal disease and acute myocardial infarction who died in the hospital was significantly higher than in patients who survived, and the AUC of the GRACE score to predict mortality hospitalization in patients with end-stage renal disease and AMI was 0.754.[35] Coronary angiography revealed that 65.8% of the subjects had multivessel disease. Another study supported this finding by revealing that CKD (GFR 60 mL/min/1.73 m^2) is associated with a 2.9-fold increased risk of multivessel coronary artery disease.[36] Although the exact mechanism is unclear, CKD is thought to hasten the progression of atherosclerosis through traditional i.e., hypertension and diabetes mellitus and non-traditional risk factors such as mineral and bone disorder disorders (CKD-MBD), anemia, inflammation chronic disease, and hyperhomocysteinemia, as well as dialysis-related factors in CKD patients on dialysis.[8,16,17]

In this study, we took secondary data from previous research as well as from medical records due to insufficient data such as data related to specific pathophysiology in other CKD, for example, CKD-MBD (phosphate, calcium, and parathyroid) and homocysteine data. Moreover, design sampling in this study was carried out consecutively. Additionally, the number of samples is not too large because the distribution of some data is not normal. However, statistical calculations indicate that the number of samples (n=117) meets the requirements. This potentially affects some of the results of the analysis which are not significant. The research was only conducted in Cipto Mangunkusumo General Hospital thus the possibility of different clinical characteristics of the patient might occur compared to other hospitals.

CONCLUSION

The incidence of MACE is higher compared to the previous studies conducted in Cipto Mangunkusumo General Hospital**.** The GRACE score has a statistically significant relationship with the 30-day MACE in ACS patients with non-dialysis CKD patients, meanwhile, the Gensini score, LVH, and NLR score had no statistically significant.

CONFLICT OF INTEREST

There is no conflict of interest.

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