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ORIGINAL RESEARCH

Cystatin C as a Predictor of Major Adverse Cardiovascular Event in Patients with Acute Myocardial Infarction Without Cardiogenic Shock and Renal Impairment After Coronary Intervention

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Purpose: To prove that cystatin C is a predictor of major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI), either with ST-segment Elevation (AMI-EST) or without ST-segment elevation (AMI-NEST), without cardiogenic shock or renal impairment.

Patient and Methods: This was an observational cohort study. Samples were obtained from AMI patients who underwent PCI between February 2022 and March 2022 at the Intensive Cardiovascular Care Unit. Cystatin C levels were measured before PCI. MACE were observed within 6 months. Comparisons between normally distributed continuous data were performed using the *t*-test; *Mann–Whitney* test was used for non-normally distributed data. Categorical data were compared using the chi-squared test. The cut-off point of cystatin C levels to predict MACE was analyzed using Receiver Operating Characteristics (ROC).

Results: The participants were 40 AMI patients, consisting of 32 patients (80%) with AMI-EST and eight patients (20%) diagnosed with AMI-NEST, who were evaluated for the occurrence of MACE within 6 months after PCI. Ten patients (25%) developed MACE during follow-up [(MACE (+)], and the rest were in the MACE (-) group. Cystatin C levels were significantly higher in the MACE (+) group (p=0.021). ROC analysis revealed a cystatin C level of 1.21 mg/dL; cystatin C > 1.21 is associated with MACE risk, showing a significant relationship with the odds ratio value reaching 26.00, with 95% CI (3.99–169.24).

Conclusion: Cystatin C level is an independent predictor of MACE in patients with AMI without cardiogenic shock or renal impairment after PCI.

Keywords: cystatin C, acute myocardial infarction, coronary intervention, cardiovascular events

Introduction

Cystatin C is a protein from the large human cystatin family and is an enzyme that prevents cysteine proteases from functioning normally. Owing to its exceptional qualities, Cystatin C was initially utilized to evaluate renal function.[1] Cystatin C has unique properties. It is regularly generated by almost all body cells, can readily pass through the glomerular filter, and is entirely reabsorbed and catabolized in the proximal renal tubule.[2] However, in recent years, cystatin C has been identified as an independent predictive biomarker of cardiovascular events, mortality, and poor outcome in patients with normal renal function. The predictive value of cystatin C is related to the concentration of cystatin C with its inflammatory effect and the formation of atherosclerosis.[3] Acute Myocardial Infarction (AMI) is the leading cause of death worldwide.[4,5] Despite the development of advanced medical sciences, such as percutaneous coronary intervention (PCI), mortality and morbidity caused by acute myocardial infarction are still relatively high.[6] According to data from Public General Hospital Dr. Moewardi Surakarta, the death rate due to AMI from 2014 to 2018 is still very high, at 15.9%.[7] Therefore, we should be able to anticipate outcomes in patients with AMI to ensure that the

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proper course of action can be taken. This study aimed to prove that cystatin C is a predictor of major adverse cardiovascular events (MACE) after PCI in patients with AMI without cardiogenic shock and renal impairment within 6 months of observation.

Materials and Methods

This was a prospective cohort study of patients with AMI who underwent PCI in the catheterization laboratory between February and March 2022 at the Intensive Cardiovascular Care Unit of Dr. Moewardi Hospital in Surakarta, Indonesia. A total of 53 patients with AMI who met the inclusion criteria were included in the study. Thirteen patients were excluded, including five patients experiencing cardiogenic shock, six patients with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, and two patients experiencing sepsis. Thus, 40 patients were qualified to be observed for the incidence of MACE within 6 months. All 40 patients were followed up for 6 months. The inclusion criteria of the study included: 1. Patients aged >18 years with AMI, AMI with ST-segment Elevation (AMI-EST), or AMI without ST-segment elevation (AMI-NEST); 2. AMI patients who were willing to be treated with the PCI. AMI is defined as an acute myocardial damage with clinical evidence of AMI in the presence of an abnormal cardiac biomarker (cardiac troponin) at least one value above the 99th percentile upper reference limit, accompanied by at least one of the following: 1) Complaints of AMI, 2) Electrocardiographic changes as evidence of new ischemia, 3) Pathological Q wave formation, 4) Imaging evidence of loss of myocardial viability or new regional myocardial wall motion abnormalities consistent with the etiology of ischemia.[8] Exclusion criteria included: chronic renal failure (eGFR < 60 mL/min/1.73 m^2, malignancy, cardiogenic shock, pregnancy, and sepsis. eGFR expression was calculated using the Cockcroft–Gault formula. The PCI was performed on AMI patients. Six months later, MACE were observed. MACE were defined as death from any cause, reinfarction, rehospitalization due to heart failure, stroke infarction, or hemorrhagic stroke, and dialysis. The clinical data of the participants were collected during hospitalization. The treatments for the participants were at the discretion of the attending cardiologists, without any interference from this research. The participants were observed for MACE from admission until 6 months after hospital discharge. Adverse cardiac events included cardiac death, acute heart failure, cardiogenic shock, reinfarction, and resuscitated ventricular arrhythmia. Cardiac death is caused by cardiac diseases. Acute heart failure was defined as the presence of signs or symptoms of congestion and the use of intravenous diuretics. Cardiogenic shock was defined as reduced peripheral perfusion and the use of vasopressor drugs. Reinfarction was defined as recurrent chest pain, recurrent ST-segment elevation, or elevated cardiac enzyme levels. Resuscitated ventricular arrhythmia was defined as the return of spontaneous circulation after resuscitation for a lethal arrhythmia. This study was approved by the Ethics Committee of Dr. Moewardi Surakarta, agreement no. 366/III/HREC/2022. Written informed consent was obtained from patients and relatives of all enrolled patients.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0. Quantitative characteristic variables are expressed in terms of the mean and standard deviation, whereas qualitative characteristic variables are described in terms of the number/frequency and proportion of each category of qualitative variables in percentages. If the numerical data were regularly distributed, the independent *t*-test was employed; otherwise, the Mann–Whitney test was applied. Categorical data were analyzed using the chi-squared or Fisher's exact tests.

Receiver operating characteristic (ROC) analysis was used to identify the optimal cut-off value for determining the prognostic value limit. The results of the ROC analysis were assessed quantitatively using the Area under the curve (AUC), 95% confidence interval (CI), and sensitivity and specificity values to obtain the best cutoff value.

Results

Forty patients qualified to be observed and followed for the incidence of MACE for 6 months. Of the 40 patients, 32 patients (80%) were diagnosed with AMI-EST and 8 patients (20%) with AMI-NEST. Within 24 h of AMI identification, coronary intervention was performed in all patients. Of the 40 patients (who made up the sample), 10 patients (25.0%) had occurred MACE at the 6-month evaluation, while the other 30 patients (75.0%) did not have MACE. MACE occurred in 10 patients with details: reinfaction of AMI occurred in 3 patients (7.5%), heart failure in 5 patients (12.5%),

stroke infarction in 1 patient (2.5%) and cardiac death in 1 patient (2.5%). One patient was not routinely monitored for evaluation, due to due to patient insurance issues, and geographic reasons.

Demographically, the age of the patients in this study generally ranged from 34 to 73 years, with a mean age value of 55.95 ± 8.51 years. The dominant sex in this study was male, with 37 men (92.5%).

History of smoking and hypertension were the most dominant risk factors in this study: 31 (77.5%) patients had a history of smoking, and 21 (52.5%) had a history of hypertension. Diabetes mellitus, stroke, dyslipidemia, and coronary artery disease (CAD) were found in thirteen (32.5%), two (5.0%), eleven (27.5%), and seven (17.5%) patients, respectively. Body mass index (BMI) values ranged from 19.95 kg/m^2 to 32.83 kg/m^2, with an average of 26.24 ± 3.37 kg/m^2.

Laboratory characteristics of hemoglobin had values ranging from 10.10 g/dL to 18.80 g/dL, with an average of 13.90 ± 1.71 g/dL; hematocrit values from 30.00 to 55.00, with an average of 40.88 ± 5.03; leukocyte values between 5.70 (10^3 /µL) and 21.90 (10^3 /µL), with an average of 12.84 ± 3.32 (10^3/µL); platelet values from 173 (10^3 /µL) to 627 (10^3 /µL), with an average value of 275.93 ± 96.53 (10^3/µL); and random blood glucose values from 11 mg/dl to 371 mg/dL, with an average of 155.05 ± 66.69 mg/dL. Creatinine values were between 0.40 mg/dL and 1.60 mg/dL, with a mean of 1.06 ± 0.32 mg/dL. Meanwhile, the eGFR ranged from 60 mL/min to 221 mL/min, with an average of 85.40 ± 35.19 mL/min. Left ventricular ejection fraction (LVEF) ranged from 17% to 59%, with an average of 43.20 ± 9.99%. The baseline clinical characteristic data for this study are shown in Table 1.

Homogeneity tests of the characteristic variables were performed to determine whether each characteristic variable was homogeneous or the same based on the 6-month MACE. The characteristic variables of this study were homogeneous according to the results of the homogeneity test. We divided the study participants into two groups: the MACE (+) group and the MACE (-) group. Based on the data on the baseline characteristics of the two groups, the patients in the MACE (+) group (59.40 ± 8.87) was older than those in the MACE (-) group (54.80 ± 8.21), although not significantly different (p = 0.141). The BMI values of both groups were similar. The incidence of Killip grades 2 and 3 in the MACE (+) group (30.0%) was higher than that in the MACE (-) group (16.7%), although the difference was not significant (p = 0.388). The MACE (+) group had

Table 1 Baseline Clinical Characteristics

Variable	**Parameter**	
	N (%)	**Mean ± SD**
Age (years)		55.95 ± 8.51
Sex:		
Male (n)	37 (92.5)	
Female (n)	3 (7.5)	
Hypertension (n)	21 (52.5)	
Diabetes mellitus (n)	13 (32.5)	
Stroke (n)	2 (5.0)	
Smoking (n)	31 (77.5)	
Dyslipidemia (n)	11 (27.5)	
CAD history (n)	7 (17.5)	
Clinical:		
BMI (kg/m2)		26.24 ± 3.37
Heart Rate (x/minute)		83.13 ± 23.35

(*Continued*)

Table 1 (Continued).

Variable	Parameter	
	N (%)	Mean ± SD
Blood parameter:		
Hemoglobin (g/dL)		13.90 ± 1.71
Hematocrit (%)		40.88 ± 5.03
Leukocyte (10^3 mcg/L)		12.84 ± 3.32
Thrombocyte (10^3 mcg/L)		275.93 ± 96.53
Random blood glucose (mg/dL)		155.05 ± 66.69
Creatinine (mg/dL)		1.06 ± 0.32
eGFR mL/min		85.40 ± 35.19
Echocardiography parameter:		
LVEF (%)		43.20 ± 9.99

Abbreviations: CAD, Coronary Artery Disease; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; LVEF, Left Ventricular Ejection Fraction.

a higher GRACE score (115.00 ± 16.83) than the MACE (-) group (104.13 ± 20.34) but not statistically significant (p = 0.137). There were no significant differences in the traditional risk factors between the MACE (+) and MACE (-) groups. There was no difference in creatinine level between the MACE (+) and MACE (-) groups (p = 0.516). Although not statistically significant (p=0.104), the MACE (+) group had a worse LVEF (37.40 ± 12.24) than the MACE (-) group (45.13 ± 8.49). For further details, please refer to Table 2.

The explanation of the cystatin C level variable based on the grouping of the MACE variable in 6 months was first provided before evaluating it as a predictor of the MACE variable. Cystatin C levels generally ranged from 0.12 to 3.50 mg/dL, with an average value of 0.93 ± 0.8 mg/dL. In the MACE (+) group, cystatin C levels ranged from 0.22 to 3.50 mg/dL, with a mean of 1.43 ± 0.89 mg/dL. Meanwhile, in the MACE (-) group, cystatin C levels ranged from 0.12 to 3.39 mg/dL with an average of 0.76 ± 0.70 mg/dL). For further details, please refer to Table 3.

Table 2 Baseline Characteristics of MACE Status Within 6 Months

Quantitative Variable	MACE (+)		MACE (-)		Prob.
	Mean/n	SD/%	Mean/n	SD/%	
Baseline:					
Age (years)[a]	59.40	8.87	54.80	8.21	0.141
Sex:[b]					
Male	9	90.0%	28	93.3%	
Female	1	10.0%	2	6.7%	
BMI (kg/m^2)[a]	26.23	3.66	26.24	3.34	0.996
Killip					0.388
Killip 1	7	70.0%	25	83.3%	

(*Continued*)

Table 2 (Continued).

Quantitative Variable	MACE (+)		MACE (-)		Prob.
	Mean/n	SD/%	Mean/n	SD/%	
Killip 2–3	3	30.0%	5	16.7%	
GRACE Score	115.00	16.83	104.13	20.34	0.137
Comorbidity					
Hypertension[b]	3	30.0%	18	60.0%	0.148
Diabetes mellitus[b]	3	30.0%	10	33.3%	1.000
Stroke[b]	0	0.0	2	6.7%	1.000
Smoking[b]	8	80.0%	23	76.7%	1.000
Dyslipidemia[b]	3	30.0%	8	26.7%	1.000
CAD	2	20.0%	5	16.7%	1.000
Blood Test					
Creatinine	1.12	0.35	1.04	0.31	0.516
Echocardiography					
LVEF Simpson (%)	37.40	12.24	45.13	8.49	0.104
Drugs					
ACE-Inhibitor	9	90.0%	26	86.7%	1.000
Statin	10	100%	30	100%	1.000
Beta Blocker	9	90.0%	27	90.0%	1.000

Notes: [a]Independent *t*-test (numerical data met the assumption of normality); [b]Chi square/fisher exact test (nominal categorical data).

Table 3 MACE Difference Result in Cystatin C Values

Variable	MACE (+)		MACE (-)		p
	Mean	SD	Mean	SD	
Cystatin C	1.43	0.89	0.76	0.70	0.021*

Notes: Mann Whitney test (numerical data do not meet the assumption of normality); *Significant, *Significant at the 5% significance level.

There appeared to be a difference in the mean cystatin C level between the MACE (+) and MACE (-) groups at a significance level of 5% ($p<0.05$). Cystatin C levels differed significantly between the MACE (+) and MACE (-) groups. Thus, cystatin C was related to or affected the occurrence of MACE.

Furthermore, ROC curve analysis can determine whether cystatin C levels predict 6-month MACE. The ROC curve for the incidence of MACE with cystatin C levels as a predictor showed an AUC value of 0.747. This indicates that MACE can be accurately detected using cystatin C levels. According to the ROC curve, the cut-off point for the cystatin C level was 1.21 mg/dL (Figure 1).

MACE occurrence can be determined from the cystatin C level with a sensitivity of 80.0%, specificity of 86.7%, and diagnostic accuracy of 85.0% when the cut-off point was set at 1.21 (Table 4).

In addition to sensitivity and specificity, cross-tabulation was used to examine the qualitative relationship between cystatin C and MACE levels using the chi-square/Fisher exact test (Table 5).

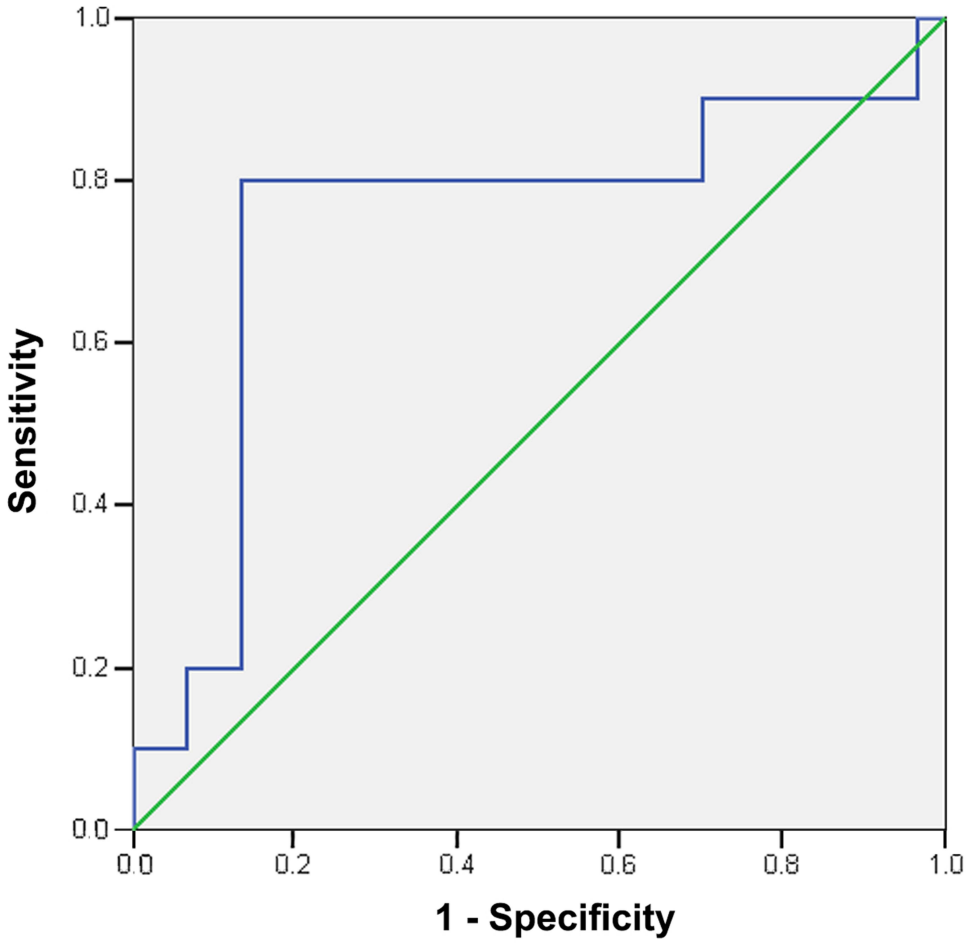

Figure 1 ROC curve for determining the cut-off point of the Cystatin C levels on the incidence of MACE (cut-off point=1.21 mg/dL). AUC value 0.747.

The relationship level of $p < 0.001$ between cystatin C levels and MACE indicated that the relationship between the two variables was significant at a 1% significance level ($p < 0.01$). The odd ratio (OR) value reached 26.00 with 95% CI (3.99–169.24), indicating that the relationship between cystatin C levels and MACE was significant. This strengthens the position of the cystatin C level as a predictive variable for the occurrence of MACE within 6 months.

Table 4 Sensitivity, Specificity, and Diagnostic Accuracy of Cystatin C

Variable	MACE in 6 Months				
	AUC	Cut-Off	Sensitivity	Specificity	Accuracy
Cystatin C	0.747	1.21	80.0%	86.7%	85.0%

Table 5 Relationship Between Cystatin C and MACE in 6 Months (Cut-off Point = 1.21)

Variable		MACE (+)		MACE (-)		*p*-value
		n	%	n	%	
Cystatin C	≥1.21 (high)	8	80.0%	4	13.3%	<0.001**
	<1.21 (low)	2	20.0%	26	86.7%	

Notes: Chi-square/Fisher's exact test; **Significant at the 1% significance level.

Discussion

AMI remains a disease with the highest cause of mortality globally.[5] Despite the development of medical science, especially in PCI, mortality and morbidity caused by AMI are still quite common.[6] Therefore, a predictor is needed to assess the incidence of MACE in AMI patients after PCI. We observed the incidence of MACE for 6 months in AMI patients undergoing PCI with good renal function and without cardiogenic shock during the treatment.

There were no discernible differences between the MACE (+) and MACE (-) groups in terms of BMI or conventional atherosclerosis risk factors. The Killip grades and GRACE scores did not differ significantly between the two groups. The MACE group showed a decreased LVEF.

Based on this study, cystatin C in the MACE (+) group had a statistically significant difference compared to the MACE (-) group. The MACE (+) group had higher cystatin C values than the MACE (-) group. High cystatin C levels were associated with a higher risk of death and MACE. This result is in line with previous studies by Precek et al and Abid et al We excluded cardiogenic shock and kidney injury from the population in this study, because in cardiogenic shock and kidney injury there is decreased blood flow to the kidneys and this would result in increased levels of Cystatin C, which would confound the study results.[9,10] In the absence of cardiogenic shock and kidney injury, higher cystatin C levels are associated with a higher incidence of MACE. This is consistent with a study by Astor et al, which stated that high cystatin C levels in the general population were associated with cardiovascular disease incidence and mortality.[11]

ROC curve analysis showed that the cystatin C value cut-off was 1.21 mg/dL for MACE, with a sensitivity of 80.0%, specificity of 86.7%, and diagnostic accuracy of 85.0%. The cut-off value of cystatin C > 1.21 mg/dL with MACE showed a significant relationship with the OR value reaching 26.00 with 95% CI (3.99–169.24), indicating that the relationship between cystatin C levels and MACE was significant. These factors strengthen the position of cystatin C level as a predictor variable for MACE within 6 months. The cut-off level of cystatin C is similar to the study by Abid et al, which is 1.20 mg/dL with 4.8 times the risk of death.[10]

The mechanism linking high cystatin C levels to the incidence of MACE has not yet been thoroughly elucidated. Renal impairment and high cystatin C levels are not entirely understood.[12] Even in studies of healthy renal function, elevated cystatin C concentrations have been associated with a higher risk of MACE. Since there is a correlation between cystatin C and C-reactive protein levels, it is assumed that cystatin signals a slight increase in inflammation.[13] Additionally, it is anticipated that cystatin C will serve as a marker for kidney health and inflammation.[14,15]

Limitation

Considering that patients from only one center were enrolled, our study has several limitations. One patient was not routinely monitored for evaluation, because of the insurance issues, and geographic reasons. Thus, patient follow-up cannot be fully monitored. Another limitation of this study is the small sample size, which is clearly insufficient to accurately describe the situation, so observation of MACE episodes may have required longer observations with a larger study sample in future studies.

Conclusion

Cystatin C can be an independent prognostic marker for MACE in AMI patients with normal renal function and without cardiogenic shock. In this study, we obtained a cut-off value of cystatin C 1.21 mg/dL for the risk of MACE.

Abbreviations

ACE-I, Angiotensin Converting Enzyme-Inhibitor; AMI-EST, Acute Myocardial infarction with Elevation ST segment; AMI-NEST, Acute Myocardial infarction with Non Elevation ST segment; AUC, Area Under Curve; ELISA, Enzyme-Linked Immunosorbent Assay; GFR, Glomerular Filtration Rate; NYHA, New York Heart Association; OR, Odd ratio; ROC, Receiver Operating Characteristic.

Ethics Approval and Consent to Participate

The study was performed according to the Declaration of Helsinki guidelines and was approved by the Ethics Committee of Dr. Moewardi hospital Surakarta, agreement no. 366/III/HREC/2022. Written informed consent was obtained from the patient or from a family member.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest in this study.

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