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Original Article

Association of interleukin-6 and C-reactive protein with in-hospital mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Abstract

Inflammation contributes substantially to the pathogenesis of acute coronary syndromes (ACS), and interleukin-6 (IL-6) and C-reactive protein (CRP) have been proposed as biomarkers of adverse outcomes. The aim of this study was to evaluate the associations of IL-6 and CRP with in-hospital mortality among patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). This prospective cohort study enrolled adult patients with STEMI who underwent primary PCI at Dr. Sardjito General Hospital, Yogyakarta, Indonesia, in 2023. A single blood sample for IL-6 and CRP measurement was collected within 24 hours after PCI. In-hospital mortality was recorded during hospitalization. Receiver operating characteristic analysis identified optimal cut-off values, and multivariable logistic regression was performed to adjust for potential confounders. In-hospital mortality occurred in 6 patients (12.8%). In univariate analysis, higher IL-6 and CRP levels were associated with in-hospital mortality. IL-6 ≥84.60 pg/mL showed an area under the curve (AUC) of 0.776, sensitivity of 66.7%, and specificity of 82.9% (p=0.007), whereas CRP ≥31.35 mg/L showed an AUC of 0.748, sensitivity of 83.3%, and specificity of 68.3% (p=0.015). However, after adjustment for confounding variables in separate multivariable models, neither IL-6 nor CRP remained independently associated with in-hospital mortality. These findings indicate that although elevated IL-6 and CRP levels were associated with in-hospital mortality in unadjusted analyses, their independent prognostic value was not retained after accounting for other clinical and laboratory factors. Further studies with larger sample sizes are needed to clarify the role of these inflammatory biomarkers in risk stratification among patients with STEMI.

Keywords: STEMI, ST-elevation myocardial infarction, in-hospital mortality, interleukin-6, C-reactive protein

Introduction

Inflammatory processes are fundamental to both the development and progression of acute coronary syndromes (ACS). Cytokines, including interleukins, tumor necrosis factors, chemokines, adipokines, and interferons, mediate inflammatory cell recruitment and platelet aggregation, thereby accelerating atherosclerotic plaque formation and destabilization and precipitating ACS. These cytokines also promote cardiomyocyte apoptosis, leading to additional

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myocardial injury, as well as progressive ventricular remodeling and dysfunction following myocardial infarction, ultimately contributing to heart failure along with a spectrum of major adverse cardiac events (MACE) leading to subsequent short-term mortality as well as overall prognosis [1,2]. Based on these pathophysiological mechanisms, multiple studies have evaluated cytokine levels as prognostic indicators in ACS [3].

Interleukin-6 (IL-6) and C-reactive protein (CRP) are widely regarded as principal indicators of inflammatory activity and are commonly utilized in clinical practice [1]. Plasma IL-6 concentrations were significantly higher in patients with coronary artery disease (CAD) and were not influenced by other cardiovascular risk factors [4]. Patients with unstable angina exhibited approximately three-fold higher plasma IL-6 levels compared with healthy controls, suggesting involvement of IL-6 in the early acute-phase response in ACS [5]. Downstream signaling through the IL-6 receptor is thought to regulate cardiomyocyte loss, as well as cardiac hypertrophy and dysfunction, thereby contributing to the prediction of subsequent cardiac events following myocardial infarction [6]. Clinical studies in patients with ACS have demonstrated an association between IL-6 and ischemia–reperfusion myocardial injury, as well as increased mortality [6,7].

CRP is a positive acute-phase reactant implicated in the development of complications after myocardial infarction, including ventricular wall and papillary muscle rupture, aneurysm formation, infarct expansion, and subsequent ventricular remodeling and dysfunction [8]. CRP levels reflect systemic inflammatory activity and function as downstream biomarkers of interleukin-mediated signaling [9]. A study demonstrated that increased CRP levels indicate persistent cardiac and low-grade systemic inflammation, playing a role in the progression to post-infarction heart failure despite optimal medical treatment [2]. High levels of high-sensitivity CRP (hs-CRP) during the early phase of ACS, prior to the onset of myocardial necrosis, are considered an important prognostic marker. Therefore, early assessment of these biomarkers during ACS may help identify patients at higher risk of developing myocardial dysfunction [10]. Since the aforementioned studies have demonstrated that higher circulating levels of IL-6 and CRP are linked to worse prognosis and increased mortality in ACS, the present study aimed to further evaluate the predictive role of these biomarkers for in-hospital mortality among patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Methods

Study design and setting

This study used a prospective cohort design. Patients with STEMI who underwent primary PCI were consecutively enrolled at Dr. Sardjito General Hospital, Yogyakarta, Indonesia, between May and July 2023. The study was conducted to evaluate the prognostic value of inflammatory biomarkers, particularly IL-6 and CRP, for in-hospital mortality in this patient population.

Sample and criteria

The study population comprised adult patients diagnosed with STEMI based on clinical presentation, biochemical findings, and electrocardiographic criteria. Eligible participants were those aged 18 years or older who underwent primary PCI during the study period. Patients were excluded if they died before blood sampling for IL-6 and CRP measurement could be performed or if they were discharged against medical advice before completion of in-hospital follow-up.

Sample size and sampling method

The minimum required sample size was calculated to provide 80% statistical power with a two-sided alpha level of 0.05, resulting in a minimum sample of 41 patients. Participant recruitment was performed using a non-probability consecutive sampling approach, in which all eligible patients admitted during the study period were invited to participate until the required sample size was reached.

Data collection procedures

The diagnosis of STEMI and the decision to perform primary PCI were made by the attending cardiologists in accordance with the 2017 European Society of Cardiology guidelines for the

management of acute myocardial infarction in patients presenting with ST-segment elevation [11]. After primary PCI, eligible patients or their legally authorized family members were approached to participate in the study. Following informed consent, a single blood sample for IL-6 and CRP measurement was collected within the first 24 hours after PCI. Other routine laboratory investigations and transthoracic echocardiography were also performed during the same period. Patients were then followed throughout hospitalization to determine in-hospital mortality.

Study variables

The dependent variable in this study was in-hospital mortality. In-hospital mortality was defined as death from any cause during hospitalization, from the time of primary PCI until discharge. The main independent variables were serum IL-6 and CRP levels measured within 24 hours after primary PCI. Other independent variables considered as potential confounders included demographic characteristics, cardiovascular risk factors, clinical presentation, echocardiographic findings, and laboratory parameters.

Approximately 10 mL of blood was drawn from each patient within the first 24 hours after PCI. The blood sample was then stored in a BD vacutainer serum separator tube for further laboratory processing. Serum IL-6 concentration was measured using an electrochemiluminescence immunoassay on the cobas e Elecsys IL-6 platform (Roche Diagnostics, Mannheim, Germany), which uses a sandwich immunoassay technique. In brief, the sample was incubated with biotinylated and ruthenium-labeled monoclonal IL-6 antibodies in the presence of streptavidin-coated microparticles, and the resulting chemiluminescent signal was measured to determine IL-6 concentration. Serum CRP level was measured using a particle-enhanced immunoturbidimetric assay with cobas c Tina-quant CRP IV (Roche Diagnostics, Mannheim, Germany). In this assay, human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The aggregates were then measured turbidimetrically.

Demographic and baseline clinical variables included age, sex, history of coronary artery disease, smoking status, hypertension, and diabetes mellitus. Clinical characteristics also included STEMI location, Killip class, cardiogenic shock, and acute heart failure. STEMI location was determined from the initial electrocardiogram obtained at presentation. Anterior STEMI was defined by ST-segment elevation in leads V1–V6, with or without involvement of leads I and aVL, whereas inferior STEMI was defined by ST-segment elevation in leads II, III, and aVF, with reciprocal ST-segment depression in leads I and aVL [12]. The severity of heart failure on admission was assessed using the Killip classification. Killip class I indicates the absence of clinical signs of heart failure; class II indicates mild heart failure, such as pulmonary rales, elevated jugular venous pressure, or a third heart sound; class III indicates acute pulmonary edema; and class IV indicates cardiogenic shock or hypotension with evidence of end-organ hypoperfusion [13]. In this study, cardiogenic shock was defined as the need for pharmacological and/or mechanical circulatory support to maintain a mean arterial pressure of at least 65 mmHg in the presence of end-organ hypoperfusion, while acute heart failure was defined as the rapid or progressive onset of signs and/or symptoms of heart failure during hospitalization [14,15].

Cardiac function was assessed by transthoracic echocardiography performed within 24 hours after PCI by trained cardiology residents and verified by senior cardiologists. Left ventricular systolic function was evaluated using left ventricular ejection fraction (LVEF) measured by the Simpson's biplane method, whereas right ventricular systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE). Reduced left ventricular function was defined as LVEF <50%, while reduced right ventricular systolic function was defined as TAPSE <17 mm, as recommended by the European Society of Cardiology [15,16].

Other laboratory parameters included blood urea nitrogen, serum creatinine, and high-sensitivity cardiac troponin T (hs-cTnT). Blood urea nitrogen was measured using UREAL for quantitative determination in human serum on Roche/Hitachi cobas c systems (Roche Diagnostics, Mannheim, Germany). Creatinine was measured using the Creatinine Jaffe Gen.2 Roche/Hitachi cobas c system (Roche Diagnostics, Mannheim, Germany), whereas hs-cTnT was measured using electrochemiluminescence immunoassay with the cobas e Elecsys Troponin T hs platform (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

All statistical analyses were performed using SPSS version 27.0 (IBM, New York, USA). Continuous variables were summarized as mean ± standard deviation or median (interquartile range), as appropriate, while categorical variables were presented as frequencies and percentages. Bivariate analyses were performed to examine the associations between each independent variable and in-hospital mortality. Because IL-6 and CRP were not normally distributed, non-parametric approaches were applied where appropriate.

Cut-off values for IL-6, CRP, and other continuous variables, including creatinine and hs-cTnT, were identified using receiver operating characteristic (ROC) curve analysis, and the optimal thresholds were determined based on the maximum Youden index. Associations between categorized variables and in-hospital mortality were then assessed using the Chi-square or Fisher's exact test, depending on the expected frequency. Variables with potential prognostic relevance identified in bivariate analysis were included in multivariable logistic regression models to adjust for confounding factors. Because of multicollinearity, IL-6 and CRP were evaluated in separate multivariable models. Correlation testing was also performed to assess the relationships between inflammatory biomarkers and hs-cTnT prior to inclusion in the regression models. A $p<0.05$ was considered statistically significant.

Results

Patients' characteristics

A total of 47 patients with STEMI who underwent primary PCI were enrolled in this study and their characteristics are presented in **Table 1**. The mean age of the patients was 59.2±9.7 years, and most were male (87.2%). Inferior STEMI was the most frequent presentation (42.5%), followed by anterior STEMI (36.2%) and combined anterior and inferior STEMI (21.3%). Most patients were classified as Killip class I on admission (74.5%), whereas 12.8% were classified as Killip class IV. Cardiogenic shock and acute heart failure were observed in 14.9% and 12.8% of patients, respectively.

Regarding cardiovascular risk factors, 68.1% of patients were ex-smokers or current smokers, 59.6% had hypertension, 31.9% had diabetes mellitus, and 4.3% had a history of coronary artery disease. Reduced left ventricular systolic function, defined as LVEF <50%, was found in 46.8% of patients, while reduced right ventricular systolic function, defined as TAPSE <17 mm, was observed in 34.0%. The median IL-6 level was 42.3 pg/mL (IQR: 20.7–78.6), and the median CRP level was 25.1 mg/L (IQR: 4.64–44.2). The median blood urea nitrogen (BUN), creatinine, and high-sensitivity troponin-T (hs-cTnT) levels were 15.0 mg/dL (IQR: 12.0–22.0), 1.2 mg/dL (IQR: 0.87–1.57), and 716 ng/L (IQR: 267–2389), respectively.

Table 1. Baseline characteristics of patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) included in the study (n=47)

Characteristics	Frequency (%)
Age (years) (mean±SD)	59.21±9.69
Sex	
Male	41 (87.2%)
Female	6 (12.8%)
Risk factors	
History of coronary artery disease	2 (4.3%)
Ex/smoker	32 (68.1%)
Hypertension	28 (59.6%)
Diabetes	15 (31.9%)
ST-elevation myocardial infarction location	
Anterior	17 (36.2%)
Inferior	20 (42.5%)
Anterior and inferior	10 (21.3%)
Killip	
I	35 (74.5%)
II	6 (12.8%)
III	0 (0.0%)
IV	6 (12.8%)
Cardiogenic shock	7 (14.9%)

Characteristics	Frequency (%)
Acute heart failure	6 (12.8%)
Reduced left ventricular ejection fraction <50%	22 (46.8%)
Reduced tricuspid annular plane systolic excursion <17 mm	16 (34.0%)
Laboratory parameters (median (interquartile range))	
Interleukin-6 (pg/mL)	42.3 (20.7–78.6)
C-reactive protein (mg/L)	25.1 (4.64–44.2)
Blood urea nitrogen (mg/dL)	15.0 (12.0–22.0)
Creatinine (mg/dL)	1.2 (0.87–1.57)
High-sensitivity troponin-T (ng/L)	716 (267–2389)

Univariate analysis showing factors associated with in-hospital mortality

In-hospital mortality occurred in six patients, yielding a mortality rate of 12.8%. Univariate analysis revealed several variables associated with in-hospital mortality, including Killip class (p=0.012) and cardiogenic shock on admission (p=0.010), impaired RV systolic function as indicated by a TAPSE <17 mm (p=0.006), as well as renal and myocardial injury biomarkers such as BUN (p=0.001) and serum creatinine (p=0.001). Diabetes mellitus (p=0.051) and hs-cTnT (p=0.056) showed borderline associations, thus were also considered for further analysis (**Table 2**).

Table 2. Univariate analysis showing factors associated with in-hospital mortality among patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI)

Characteristics	Group		p-value
	Survived (n=41)	Died (n=6)	
	n (%)	n (%)	
Age (years) (mean±SD)	59.49±9.96	57.33±8.04	0.616
Sex			0.759
Male	36 (87.8%)	5 (12.2%)	
Female	5 (83.3%)	1 (16.7%)	
Risk factors			
History of coronary artery disease	2 (100.0%)	0 (0.0%)	0.580
Ex/smoker	28 (87.5%)	4 (12.5%)	0.936
Hypertension	26 (92.9%)	2 (7.1%)	0.161
Diabetes	11 (73.3%)	4 (26.7%)	0.051*
ST-elevation myocardial infarction location			0.917
Anterior	15 (88.2%)	2 (11.8%)	
Inferior	17 (85.0%)	3 (15.0%)	
Anterior and inferior	9 (90.0%)	1 (10.0%)	
Killip			0.012**
I	32 (91.4%)	3 (8.6%)	
II	6 (100.0%)	0 (0.0%)	
III	0	0	
IV	3 (50.0%)	3 (50.0%)	
Cardiogenic shock	4 (57.1%)	3 (42.9%)	0.010**
Acute heart failure	5 (83.3%)	1 (16.7%)	0.759
Reduced left ventricular ejection fraction <50%	18 (81.8%)	4 (18.2%)	0.297
Reduced TAPSE <17 mm	11 (68.8%)	5 (31.2%)	0.006**
Laboratory parameters (median (IQR))			
Interleukin-6 (pg/mL)	29.8 (18.8–72.7)	152.8 (46.4–1824.0)	0.029**
C-reactive protein (mg/L)	18.4 (2.4–41.2)	39.6 (25.1–237.8)	0.052*
Blood urea nitrogen (mg/dL)	15.0 (12.0–19.5)	41.5 (33.0–59.0)	0.001**
Creatinine (mg/dL)	1.2 (0.9–1.3)	2.5 (1.6–4.4)	0.001**
High-sensitivity troponin-T (ng/L)	634 (227–1823)	3137 (1641–7535)	0.056*

IQR: interquartile range; TAPSE: tricuspid annular plane systolic excursion
*p<0.1, considered for multivariable analysis
**Statistically significant at p<0.05

Predictive values of the role of interleukin-6 (IL-6) and C-reactive protein (CRP) for in-hospital mortality

Both IL-6 and CRP were significantly associated with in-hospital mortality (**Table 3**). Interleukin-6 had an optimal cut-off value of ≥84.60 pg/mL, yielding a sensitivity of 66.7% and a specificity of 82.9% (p=0.007), while CRP had an optimal cut-off value of ≥31.35 mg/L, yielding a sensitivity of 83.3% and a specificity of 68.3% (p=0.015). Overall, ROC analysis for both

biomarkers demonstrated moderate discriminatory ability for in-hospital mortality. Interleukin-6 yielded an AUC of 0.776 (95%CI: 0.561–0.992), while CRP yielded an AUC of 0.748 (95%CI: 0.544–0.952), suggesting a slightly better predictive performance for IL-6 than for CRP (**Figure 1**).

Table 3. Receiver operating characteristic (ROC) analysis identified interleukin-6 (IL-6) and C-reactive protein (CRP) cut-off values associated with in-hospital mortality

Biomarker	Area under the curve (AUC)	Cut-off	Sensitivity (%)	Specificity (%)	*p*-value
Interleukin-6 (pg/mL)	0.776	≥84.60	66.7	82.9	0.007**
C-reactive protein (mg/L)	0.748	≥31.35	83.3	68.3	0.015**

**Statistically significant at $p<0.05$

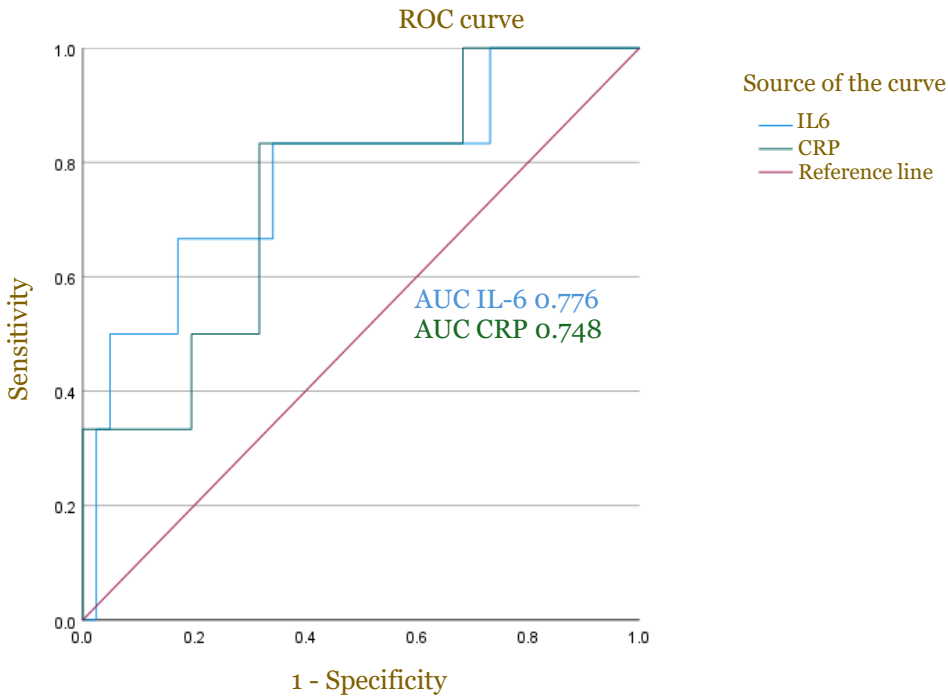

Figure 1. Receiver operating characteristic (ROC) curves of interleukin-6 (IL-6) and C-reactive protein (CRP) for in-hospital mortality. The area under the curve (AUC) was 0.776 (95%CI: 0.561–0.992) for IL-6 and 0.748 (95%CI: 0.544–0.952) for CRP, indicating moderate discriminatory ability for both biomarkers.

Multivariate analysis showing the association between interleukin-6 (IL-6) and C-reactive protein (CRP) with in-hospital mortality

Multivariable logistic regression models were constructed to adjust for potential confounders identified in the univariate analyses. Because of multicollinearity among the predictors, IL-6 and CRP were entered into separate multivariable models. Blood urea nitrogen was excluded from the multivariable analyses for the same reason. The cut-off values, determined by the maximum Youden index from the ROC curve analysis, were ≥1.3 mg/dL for creatinine and ≥2097 ng/L for hs-cTnT. Since previous studies have suggested possible associations between hs-cTnT and inflammatory biomarkers [17,18], Pearson correlation tests were performed to assess potential collinearity prior to model fitting. A weak positive correlation was observed between hs-cTnT and CRP (r=0.289, p=0.049), whereas no significant correlation was found between hs-cTnT and IL-6 (r=-0.024, p=0.874). Therefore, hs-cTnT was retained as an adjusting variable in both multivariable models. After adjustment, neither IL-6 nor CRP remained independently associated with in-hospital mortality at the specified cut-off values (**Table 4** and **Table 5**).

Table 4. Multivariate analysis showing the association between interleukin-6 (IL-6) and other predictors with in-hospital mortality

Variables	Odds ratio	95% confidence interval		*p*-value
		Lower	Upper	
Interleukin-6, ≥84.60 pg/mL	5.29	0.22	126.02	0.303
Cardiogenic shock presence	30.06	0.36	2519.59	0.132
Diabetes presence	2.17	0.09	54.56	0.638
Killip class, >I	15.69	0.24	1020.98	0.196
TAPSE, <17 mm	10.86	0.32	369.77	0.185
Creatinine, ≥1.3 mg/dL	23.86	0.36	1573.46	0.138
High-sensitivity troponin-T, ≥2097 ng/L	70.86	0.70	7142.29	0.070

TAPSE: tricuspid annular plane systolic excursion

Table 5. Multivariate analysis showing the association between C-reactive protein (CRP) and other predictors with in-hospital mortality

Variables	Odds ratio	95% confidence interval		*p*-value
		Lower	Upper	
C-reactive protein ≥31.35 mg/L	1.80	0.06	58.53	0.740
Cardiogenic shock presence	15.73	0.32	768.26	0.165
Diabetes presence	1.10	0.04	31.66	0.956
Killip class, >I	5.30	0.13	212.45	0.376
TAPSE, <17 mm	21.01	0.56	793.54	0.100
Creatinine, ≥1.3 mg/dL	14.46	0.29	720.08	0.180
High-sensitivity troponin-T, ≥2097 ng/L	70.84	0.86	5846.97	0.058

TAPSE: tricuspid annular plane systolic excursion

Discussion

This study examined the roles of IL-6 and CRP as inflammatory biomarkers to predict in-hospital mortality among STEMI patients undergoing primary PCI. Although higher levels of both biomarkers were associated with in-hospital mortality in unadjusted analyses, these associations did not persist after adjustment for relevant confounders. In line with these findings, previous studies have also reported uncertainty about the prognostic relevance of inflammatory biomarkers in ACS, with conflicting results [19-26].

In the unadjusted analysis of this study, IL-6 levels ≥84.6 pg/mL were significantly associated with in-hospital mortality, with a moderate AUC of 0.776. Multiple prior investigations have also linked elevated IL-6 concentrations to unfavorable clinical outcomes, including increased mortality. A previous study demonstrated that IL-6 was a strong indicator of infarct size in patients with STEMI, reporting an AUC of 0.941 (p<0.001) [19]. Another study consistently demonstrated that early measurement of circulating cytokines—including IL-6—within 48 hours of symptom onset in STEMI patients undergoing primary PCI was correlated with impaired left ventricular systolic function and a higher incidence of MACE [20]. Other studies have also reported that higher serum IL-6 levels are highly predictive of severe CAD [21,22].

A study examining the usefulness of serial measurement of IL-6 and CRP to predict outcomes in patients with non–ST–segment elevation acute coronary syndromes (NSTE-ACS) reported that day-1 IL-6 concentrations were independently associated with MACE, even after accounting for established prognostic variables [23]. Specifically, IL-6 levels exceeding the median threshold (>8.24 pg/mL) were associated with an increased risk of MACE (HR=1.290; p=0.027), and each 1 pg/mL increase in IL-6 was associated with an additional risk (HR=1.050; p<0.001). Conversely, neither baseline hs-CRP concentrations nor their temporal changes were independently associated with adverse outcomes in this cohort [23].

CRP concentrations ≥31.35 mg/L were significantly associated with an increased risk of in-hospital mortality in the present study, although the AUC value was also moderate at 0.748. A meta-analysis examining the predictive role of CRP in patients with acute MI undergoing PCI had demonstrated that elevated CRP concentrations were robustly associated with increased risk of both overall and cardiovascular-specific mortality [24]. Subgroup analyses in this meta-analysis further indicated that CRP had greater predictive value for rehospitalization and adverse events within the first 12 months than for longer-term outcomes, and demonstrated stronger prognostic

performance in Asian populations [24]. Consistent with these results, a single-center prospective cohort study also found that elevated hs-CRP on admission independently predicted in-hospital MACE (≥2.75 mg/L) and mortality (≥7 mg/L) in STEMI patients, even after adjustment for age, BUN, and glucose levels [25].

Collectively, these findings support the utility of inflammatory biomarkers—particularly IL-6—in reflecting the magnitude of the inflammatory response and the severity of myocardial injury in ACS. The SIESTA study, however, examined IL-6, hs-CRP, and other inflammatory markers for their prognostic value in low- to intermediate-risk NSTE-ACS patients, and found that these markers did not provide independent prognostic information. Notably, clinical outcomes in this study were assessed at 6 and 12 months of follow-up [26].

It should be noted that none of the studies mentioned above included troponin levels as confounders in their multivariate analyses. Previous literature suggests that troponin is a circulating biomarker of myocardial injury, while IL-6 and CRP represent markers of inflammation. Earlier research has produced conflicting results concerning the correlation between these biomarkers. A cross-sectional study reported a significant correlation between increases in hs-cTnT and IL-6 levels in asymptomatic hemodialysis patients and found that hs-cTnT levels were also associated with diabetes, hypertension, prior CAD, cerebrovascular events, advanced age at presentation, and male sex. These findings suggest that inflammation, as reflected by IL-6, may contribute to elevated hs-cTnT levels [17]. Another study found a positive association between IL-6 and CRP concentrations in patients with ACS. The correlation was statistically nonsignificant in the NSTE-ACS population, whereas it was significant in patients with STEMI. However, serum IL-6 concentrations were not correlated with cardiac troponin levels across any ACS subgroup [18]. Nevertheless, this perceived correlation might explain why previous studies did not include these biomarkers in a single multivariate analysis model.

In the present study, hs-cTnT is associated with in-hospital mortality, with a higher median hs-cTnT concentration found in those who died. Pearson analysis found no meaningful correlation between hs-cTnT and IL-6, and only a weak association with CRP. Therefore, hs-cTnT was retained as an adjustment variable in the multivariable models. After adjustment, the associations between IL-6 and CRP with in-hospital mortality lost their statistical significance, whereas hs-cTnT showed a stronger trend toward an association with mortality. This finding adds to the heterogeneity reported in the prior literature, in which hs-cTnT has been shown to influence mortality independently of IL-6 and CRP. Since inflammation and myocardial injury following STEMI are complex processes, investigating multiple biomarkers may thus help predict patient prognosis more accurately.

Beyond myocardial injury biomarkers, the relationship between inflammation and clinical severity may also be reflected in the occurrence of cardiogenic shock during ACS. Enhanced systemic inflammatory response was found to be more prevalent in patients with advanced cardiogenic shock, with several inflammatory indices having been found to be associated with an increased risk of mortality during hospitalization [27,28]. In one non-randomized prospective study, the mean IL-6 level was found to be higher in ACS patients with higher Killip class [29]. Due to these perceived associations, targeting the excessive early phase inflammation is therefore thought to be a potential new frontier in preventing the deterioration of ACS patients to cardiogenic shock [30,31]. However, identification of the inflammatory phenotype is important to facilitate the development of these targeted therapeutic strategies [32].

Previous studies have highlighted the potential role of drugs targeting inflammatory receptors in patients with STEMI [33,34]. The ASSAIL-MI trial investigated the role of tocilizumab, an IL-6 receptor antagonist, in enhancing myocardial salvage in patients with STEMI. The administration of tocilizumab was associated with increased myocardial salvage and reduced microvascular obstruction compared with placebo, with no significant difference in final infarct size between groups [33]. Other clinical trials evaluating the recombinant IL-1 receptor antagonist anakinra demonstrated that short-term IL-1 inhibition for 14 days in STEMI patients treated successfully with PCI was associated with a significant decrease in composite outcomes, including new-onset heart failure or mortality, and heart failure–related hospitalization or mortality, at 1-year follow-up [34]. Collectively, these studies indicate that inflammatory

pathways influence the extent of myocardial ischemia and necrosis, suggesting that targeted interventions modulating these pathways may improve outcomes after STEMI.

Our study had several limitations. Regarding the study design, prospective studies with larger cohorts and extended follow-up would be preferable to better understand relationships among variables and to ensure that the study findings capture the diverse clinical conditions of the STEMI population. Previous studies highlighted the association between IL-6 and CRP with other major clinical adverse outcomes, including heart failure [20-23,25]. Although it is known that those clinical outcomes are associated with short- and long-term prognosis, they are not assessed separately in this study, which focuses only on in-hospital mortality. To control for confounders, a further multivariate analysis was performed, including other comorbidities, clinical conditions, and biochemical markers associated with the outcomes. However, the power of the analysis was low due to the limited sample sizes, along with only a small number of in-hospital mortality events.

Previous evidence has shown that IL-6 fluctuates over time. Since IL-6 levels decline following the acute phase, serial measurements can enhance prognostic risk stratification [23]. It should be noted that the biomarker samples in our study were collected after primary PCI and thus were not obtained at the time of chest pain onset. This may have influenced circulating IL-6 and CRP concentrations and, consequently, the derived cut-off thresholds. These limitations should be noted when interpreting the results of this study and further explored in future studies.

Conclusion

Heightened inflammatory activity has been linked to myocardial damage and adverse clinical outcomes in ACS. The present findings suggest that acute, early-phase inflammation is associated with short-term prognosis. Although elevated IL-6 and CRP levels correlated with in-hospital mortality in unadjusted analyses, these associations lost statistical significance after multivariable adjustment, suggesting that the observed relationships may be influenced by confounding factors. Consequently, additional studies are warranted to clarify the precise role of these biomarkers in STEMI, determine their utility for risk stratification, and explore their potential implications for clinical management and targeted therapeutic strategies.

Ethics approval

The study protocols were conducted in accordance with the Declaration of Helsinki and were approved by the Medical and Health Research Ethics (MHREC) of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito General Hospital, Indonesia (No: KE/FK/0515/EC/2023). The study's aims, risks, and benefits were explained to each participant, and they were asked to sign a consent form before enrolment. Participants were also informed that they could quit at any time. Participation in this study was voluntary, and no incentives were provided.

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Competing interests

All authors declare no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tool, ChatGPT, to refine the language (improving grammar, sentence structure, and the manuscript's readability). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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