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Intracoronary Versus Peripheral Interleukin-6 and Myocardial Injury in STEMI Patients undergoing Primary PCI

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ABSTRACT: Interleukin-6 (IL-6) mediates myocardial and reperfusion injury in ST-segment elevation myocardial infarction (STEMI), but whether IL-6 in the culprit coronary artery reflects the degree of myocardial injury better than systemic IL-6 is unclear. We compared intracoronary and peripheral IL-6 concentrations and their correlation with high-sensitivity troponin I (hs-TnI) in STEMI patients undergoing primary percutaneous coronary intervention (PPCI). This prospective observational study enrolled 115 consecutive STEMI patients with symptom onset <24 hours who underwent PPCI at a tertiary hospital in Makassar, Indonesia. Peripheral blood was obtained at admission and intracoronary blood from the culprit artery during PPCI; IL-6 was measured by immunoassay and myocardial injury was quantified by peak hs-TnI. Mean age was 55.2 ± 9.6 years; 85.2% of patients were men. Median peak hs-TnI was 4,290 ng/L. Intracoronary and peripheral IL-6 differed significantly (median 0.64 vs 1.00 pg/mL; p = 0.013). Intracoronary IL-6 was higher in the high hs-TnI group (n = 57) than in the low hs-TnI group (n = 58) (median 2.00 vs 0.35 pg/mL; p = 0.013), whereas peripheral IL-6 did not differ (2.00 vs 1.00 pg/mL; p = 0.085). Intracoronary IL-6 correlated weakly but significantly with peak hs-TnI (r = 0.209; p = 0.025), whereas peripheral IL-6 did not (r = 0.155; p = 0.099). Culprit-artery IL-6 therefore differs from systemic IL-6 and is more closely related to the degree of myocardial injury, suggesting that local coronary inflammation reflects infarct severity better than systemic inflammation.

1. INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) remains a leading cause of death and disability worldwide, with a pooled global prevalence of myocardial infarction of approximately 3% in adults (Byrne et al., 2023; Salari et al., 2023; Vogel et al., 2019). In Indonesia, registry data show that the use of primary percutaneous coronary intervention (PPCI) has increased substantially over the past decade, although a large proportion of patients still present late or remain non-reperfused (Dharma et al., 2015), and in eastern Indonesia most STEMI patients are latecomers with a high incidence of adverse events within six months (Alkatiri et al., 2025). PPCI is the reperfusion strategy of choice for STEMI (Byrne et al., 2023; Ibanez et al., 2018); however, the restoration of coronary flow itself triggers ischaemia–reperfusion injury, which may account for a considerable part of the final infarct size and limits the benefit of timely reperfusion (Heusch, 2020).

Inflammation is central to atherothrombosis as well as to the injury, repair and remodelling that follow myocardial infarction (Frangogiannis, 2014; Hansson, 2005; Montecucco et al., 2016; Prabhu and Frangogiannis, 2016). Interleukin-6 (IL-6) is a pleiotropic cytokine produced by monocytes/macrophages, endothelial cells, vascular smooth muscle cells and ischaemic cardiomyocytes, and it is the principal upstream driver of the hepatic acute-phase response (Su et al., 2021). Elevated circulating IL-6 predicts future myocardial infarction in apparently healthy men (Ridker et al., 2000) and cardiovascular events in the general population (Khan et al., 2024), and after an acute coronary syndrome it predicts major adverse cardiovascular events independently of high-sensitivity troponin and other established biomarkers (Fanola et al., 2017; Yang et al., 2021). In STEMI specifically, plasma IL-6 correlates with peak troponin, infarct size on cardiac magnetic resonance, microvascular obstruction, left ventricular dysfunction and adverse clinical events (Groot et al., 2019; Ritschel et al., 2014; Scărlătescu et al., 2022; Tiller et al., 2022; Tøllefsen et al., 2021).

Most of these studies measured IL-6 in peripheral venous blood, which integrates hepatic, adipose and systemic production and may not reflect the inflammatory activity at the culprit lesion. Transcoronary sampling studies have demonstrated that inflammation in acute coronary syndromes is, at least in part, generated locally: neutrophil activation is widespread across the coronary bed in unstable angina (Buffon et al., 2002), IL-6 and serum amyloid A are higher at the site of the ruptured plaque than in the aorta (Maier et al., 2005), IL-6 in the infarct-related artery exceeds peripheral venous levels and is associated with restenosis and matrix metalloproteinase activation (Funayama et al., 2006; Suzuki et al., 2008), and coronary sinus sampling indicates cardiac release of IL-6 during acute coronary syndromes (Deliargyris et al., 2000). Intracoronary IL-6 has also been linked to the no-reflow phenomenon after primary angioplasty (Borrayo Sánchez et al., 2017). Nevertheless, data directly comparing intracoronary and peripheral IL-6 in relation to the degree of myocardial injury, as quantified by high-sensitivity cardiac troponin I (hs-TnI), the preferred biomarker of myocardial injury whose peak concentration reflects infarct extent (Haizler et al., 2025; Sandoval et al., 2020; Thygesen et al., 2019), are scarce, particularly in Southeast Asian populations.

This study therefore aimed to compare IL-6 concentrations in intracoronary and peripheral blood of STEMI patients undergoing PPCI, to compare both compartments according to the degree of myocardial injury, and to evaluate the correlation of intracoronary and peripheral IL-6 with peak hs-TnI.

2. MATERIALS AND METHODS

2.1 Study design and setting

This was a prospective observational analytical study conducted at the Integrated Heart Centre (Pusat Jantung Terpadu) of Dr. Wahidin Sudirohusodo General Hospital, Makassar, a tertiary referral and teaching hospital serving eastern Indonesia. Patients were recruited consecutively from February 2024 until the required sample size was reached.

2.2 Participants

The source population comprised all patients admitted to the emergency department of the Integrated Heart Centre with a diagnosis of STEMI. STEMI was diagnosed according to the European Society of Cardiology criteria (Byrne et al., 2023; Ibanez et al., 2018): ischaemic symptoms with persistent ST-segment elevation in at least two contiguous electrocardiographic leads (or new left bundle branch block) and a rise of cardiac troponin. Patients were eligible if they were older than 18 years, presented within 24 hours of symptom onset and underwent PPCI according to the hospital's standard operating procedure. Patients who died before PPCI could be performed, patients with myocardial infarction with non-obstructive coronary arteries (MINOCA)

at angiography and patients with evidence of active infection were excluded. Patients in whom the intracoronary or peripheral sample could not be obtained, or whose sample was haemolysed or otherwise damaged, were withdrawn from analysis.

2.3 Sample size

The minimum sample size was calculated for a correlation design with an anticipated correlation coefficient of 0.20 and a two-sided α of 0.05 using an online calculator (sample-size.net), yielding 96 subjects. A total of 115 patients fulfilled the criteria and were analysed.

2.4 Study procedures and laboratory measurements

On admission to the emergency department, baseline clinical data were recorded and peripheral venous blood was drawn for routine haematology (leukocyte, neutrophil and lymphocyte counts, platelets, haemoglobin and haematocrit), clinical chemistry (aspartate and alanine aminotransferase, urea and creatinine), hs-TnI and IL-6. PPCI was performed by consultant interventional cardiologists according to standard practice; after the culprit artery had been engaged and the occlusion assessed angiographically, 2–3 mL of intracoronary blood was aspirated from the culprit artery through the catheter before balloon angioplasty and/or drug-eluting stent implantation. Intracoronary samples were collected into polypropylene tubes containing ethylenediaminetetraacetic acid (EDTA) and transported to the hospital laboratory for processing according to the standard protocol.

IL-6 was measured in plasma by immunoassay and expressed in pg/mL. hs-TnI was measured in serum and expressed in ng/L at admission and serially thereafter, and the peak concentration after PPCI was used to quantify the degree of myocardial injury. All patients were followed up for 30 days by direct interview, telephone or at the outpatient clinic; clinical outcomes were not the subject of the present analysis.

2.5 Operational definitions

The degree of myocardial injury was defined as the peak hs-TnI concentration. For group comparisons, patients were classified into a high hs-TnI group and a low hs-TnI group. Diabetes mellitus was defined as a documented diagnosis in the medical record and/or current use of antidiabetic medication, supported by plasma glucose values fulfilling the diagnostic criteria for diabetes. Hypertension was defined as a documented diagnosis and/or current use of antihypertensive medication, or a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Sex was recorded as documented in the medical record and age was calculated from the date of birth on the official identity document.

2.6 Statistical analysis

Data were managed and analysed with SPSS Statistics version 28 for Mac (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed with the Kolmogorov–Smirnov test. Normally distributed variables are presented as mean ± standard deviation (SD) and non-normally distributed variables as median with interquartile range (IQR) or minimum–maximum; categorical variables are presented as frequency and percentage. Because IL-6 and hs-TnI were not normally distributed, paired intracoronary and peripheral IL-6 concentrations were compared with the Wilcoxon signed-rank test, IL-6 concentrations between the high and low hs-TnI groups were compared with the Mann–Whitney U test, and the correlation between IL-6 and peak hs-TnI was assessed with Spearman's rank correlation coefficient (r). A two-sided p value <0.05 was considered statistically significant.

2.7 Ethical approval

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin / Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia (approval No. 598/UN4.6.4.5.31/PP36/2023, dated 29 August 2023; extension No. 142/UN4.6.4.5.31/PP36/2025, dated 28 February 2025; protocol No. UH23070470). The study was conducted in accordance with the Declaration of Helsinki and local regulations, and written informed consent was obtained from all participants or their legal representatives.

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3. RESULTS AND DISCUSSION

3.1 Characteristics of the study subjects

A total of 115 STEMI patients who underwent PPCI were analysed (**Table 1**). The mean age was 55.21 ± 9.61 years and the majority were men (98 patients, 85.2%; women 17, 14.8%). Hypertension was present in 69 patients (60.0%) and diabetes mellitus in 24 (20.9%). The median peak hs-TnI was 4,290 ng/L (IQR 36,143.2 ng/L). The median IL-6 concentration was 0.64 pg/mL (IQR 2.86 pg/mL) in intracoronary blood and 1.00 pg/mL (IQR 6.77 pg/mL) in peripheral blood; both IL-6 and hs-TnI were markedly right-skewed.

Table 1. Baseline characteristics of the study subjects (n = 115)

Characteristic	Value
Age (years), mean ± SD[a]	55.21 ± 9.61
Sex, n (%)	
Men	98 (85.2)
Women	17 (14.8)
Hypertension, n (%)	69 (60.0)
Diabetes mellitus, n (%)	24 (20.9)
Peak hs-TnI (ng/L), median (IQR)[b]	4,290 (36,143.2)
Intracoronary IL-6 (pg/mL), median (IQR)[b]	0.64 (2.86)
Peripheral IL-6 (pg/mL), median (IQR)[b]	1.00 (6.77)

[a] Normally distributed data; [b] non-normally distributed data. SD = standard deviation; IQR = interquartile range; hs-TnI = high-sensitivity troponin I; IL-6 = interleukin-6.

3.2 Comparison of intracoronary and peripheral IL-6

Paired comparison of the two compartments is shown in **Table 2**. Intracoronary IL-6 (median 0.64 pg/mL, range 0.00–14,431 pg/mL) differed significantly from peripheral IL-6 (median 1.00 pg/mL, range 0.00–9,655 pg/mL; Wilcoxon Z = −2.493, p = 0.013). The distribution of intracoronary IL-6 was wider than that of peripheral IL-6, and the highest concentrations in the cohort were recorded in intracoronary samples.

Table 2. Comparison of intracoronary and peripheral interleukin-6 concentrations in STEMI patients (n = 115)

Variable	Intracoronary, median (min–max)	Peripheral, median (min–max)	Z	p value[a]
IL-6 (pg/mL)	0.64 (0.00–14,431)	1.00 (0.00–9,655)	−2.493	0.013

[a] Wilcoxon signed-rank test (paired). STEMI = ST-segment elevation myocardial infarction; IL-6 = interleukin-6.

3.3 IL-6 according to the degree of myocardial injury

Table 3 presents IL-6 concentrations according to the degree of myocardial injury. In the high hs-TnI group (n = 57), the median intracoronary IL-6 was 2.00 pg/mL (range 0.00–14,431 pg/mL) compared with 0.354 pg/mL (range 0.00–29.0 pg/mL) in the low hs-TnI group (n = 58); this difference was statistically significant (Z = −2.490, p = 0.013). Peripheral IL-6 was also

numerically higher in the high hs-TnI group (median 2.00 pg/mL, range 0.051–9,655 pg/mL) than in the low hs-TnI group (median 1.00 pg/mL, range 0.00–99.0 pg/mL), but the difference did not reach statistical significance (Z = −1.722, p = 0.085).

Table 3. Intracoronary and peripheral interleukin-6 concentrations according to the degree of myocardial injury

Variable	High hs-TnI (n = 57), median (min–max)	Low hs-TnI (n = 58), median (min–max)	Z	p value[a]
Peripheral IL-6 (pg/mL)	2.00 (0.051–9,655)	1.00 (0.00–99.0)	−1.722	0.085
Intracoronary IL-6 (pg/mL)	2.00 (0.00–14,431)	0.354 (0.00–29.0)	−2.490	0.013

[a] Mann–Whitney U test. hs-TnI = high-sensitivity troponin I; IL-6 = interleukin-6.

3.4 Correlation of IL-6 with peak hs-TnI

Spearman's rank correlation between IL-6 and peak hs-TnI is summarised in **Table 4**. Intracoronary IL-6 showed a weak but statistically significant positive correlation with hs-TnI (r = 0.209, p = 0.025), indicating that higher local IL-6 concentrations tended to accompany greater myocardial injury. The correlation between peripheral IL-6 and hs-TnI was positive but very weak and not statistically significant (r = 0.155, p = 0.099).

Table 4. Correlation of intracoronary and peripheral interleukin-6 with peak high-sensitivity troponin I in STEMI patients (n = 115)

Variable	r[a]	p value
Peripheral IL-6	0.155	0.099
Intracoronary IL-6	0.209	0.025

[a] Spearman's rank correlation coefficient. STEMI = ST-segment elevation myocardial infarction; IL-6 = interleukin-6.

3.5 Discussion

In this cohort of 115 STEMI patients treated with PPCI, IL-6 concentrations in the culprit coronary artery differed significantly from those in peripheral venous blood; intracoronary, but not peripheral, IL-6 was significantly higher in patients with a greater degree of myocardial injury; and only intracoronary IL-6 was significantly, albeit weakly, correlated with peak hs-TnI. Taken together, these findings suggest that the inflammatory signal measured at the site of the culprit lesion is more closely related to the extent of myocardial damage than the systemic inflammatory signal.

The demographic profile of our cohort, with a strong male predominance (85.2%) and a mean age of 55 years, closely matches the prospective STEMI cohort recruited earlier at the same centre (mean age 57.1 years, 80.5% men) (Alkatiri et al., 2025) and the pattern reported for STEMI elsewhere in Indonesia (Daniel et al., 2022; Dharma et al., 2015), in whom the first infarction tends to occur about a decade earlier than in Western cohorts, where mean ages above 60 years are typical (Haizler et al., 2025). Hypertension (60.0%) and diabetes mellitus (20.9%) were common, in line with the risk-factor burden of acute coronary syndrome patients in the region (Alkatiri et al., 2025). The lower proportion and later presentation of women reflect the relative protection conferred by oestrogen before the menopause and the sex-specific differences in presentation and pathophysiology described in the American Heart Association scientific statement on myocardial infarction in women (Mehta et al., 2016).

The median peak hs-TnI in our patients (4,290 ng/L) was of the same order as the median hs-TnI used to dichotomise STEMI patients treated with PPCI at Dr. Sardjito Hospital, Yogyakarta (2,063.8, reported as ng/mL), where hs-TnI above the median was associated with major adverse cardiovascular events, acute heart failure and mortality (Daniel et al., 2022), but considerably lower than the mean peak values reported in large contemporary STEMI cohorts with daily serial sampling (Haizler et al., 2025). Peak hs-TnI after reperfused STEMI depends on the sampling schedule, the time from symptom onset to reperfusion and the assay used, and in most patients hs-TnI follows a monophasic course peaking roughly 10–12 hours after PPCI (Haizler et al., 2025). Because our protocol was not designed to capture the true peak in every patient, the degree of myocardial injury may

have been underestimated in some, which would tend to weaken rather than exaggerate the associations observed. Nevertheless, peak hs-TnI remains a widely used surrogate of infarct size and is endorsed by the universal definition of myocardial infarction for the characterisation of myocardial injury (Sandoval et al., 2020; Thygesen et al., 2019).

The absolute IL-6 concentrations in both compartments were low and highly dispersed, with medians of approximately 1 pg/mL and a substantial number of values close to the detection limit, whereas European STEMI cohorts sampled within hours of symptom onset have reported median plasma IL-6 in the range of tens of pg/mL (Tiller et al., 2022; Tøllefsen et al., 2021). Several factors may explain this discrepancy. IL-6 rises within hours of coronary occlusion and peaks at approximately 24–48 hours, so that samples obtained at admission, often early after symptom onset, may capture the ascending limb of the response; assay platforms differ in their calibration and lower limits of detection; and differences in body composition, comorbidity and pre-hospital medication may modulate the systemic response (Su et al., 2021; Wainstein et al., 2017). These considerations caution against direct comparison of absolute values across studies but do not affect within-patient comparisons between compartments, which were the primary interest of this study.

Our principal finding is that intracoronary and peripheral IL-6 cannot be used interchangeably. The existence of a transcoronary gradient of inflammatory mediators has been demonstrated previously: Maier et al. (2005) found that IL-6 and serum amyloid A obtained under distal balloon occlusion at the site of the ruptured plaque were higher than aortic levels, indicating local production of biologically active IL-6; Funayama et al. (2006) and Suzuki et al. (2008) reported higher IL-6 in the infarct-related artery than in the peripheral vein, with associations with restenosis and matrix metalloproteinase activation; and Deliargyris et al. (2000) showed cardiac release of IL-6 by coronary sinus sampling in acute coronary syndromes. Buffon et al. (2002) further demonstrated that neutrophil activation is widespread across the coronary bed in unstable angina, irrespective of the location of the culprit stenosis, suggesting that coronary inflammation is a pan-coronary rather than a strictly lesion-confined process. In our cohort the overall medians favoured the peripheral compartment, whereas in patients with greater myocardial injury the medians were equal and the most extreme concentrations were intracoronary. The direction of the paired difference therefore appears to depend on the severity of injury, and the overall difference should not be interpreted simply as a uniform excess of IL-6 in one compartment. Methodological factors are likely to contribute: peripheral blood was drawn at admission, whereas intracoronary blood was obtained later during PPCI, after loading with antiplatelet agents and heparin; intracoronary blood aspirated through the catheter proximal to an occluded culprit lesion is largely arterial blood from the systemic circulation rather than blood that has perfused the lesion microenvironment, in contrast to the distal sampling under balloon occlusion used by Maier et al. (2005); and dilution by contrast medium and flush solutions may lower measured concentrations. These differences in sampling site and timing may also explain why the local signal, although more informative, was not uniformly higher.

The more important observation is the relationship between local IL-6 and the degree of myocardial injury. Intracoronary IL-6 was significantly higher in the high hs-TnI group and correlated positively with peak hs-TnI, whereas peripheral IL-6 showed the same direction of association without reaching significance. This is in keeping with the concept that inflammatory activity at the culprit lesion contributes to the extent of infarction. Borrayo Sánchez et al. (2017) found that intracoronary IL-6 was associated with the no-reflow phenomenon after primary angioplasty, and Reindl et al. (2017) showed that inflammatory markers relate to both myocardial and microvascular injury after reperfused STEMI. In large peripheral-blood studies, IL-6 correlated with peak troponin T in more than 1,000 STEMI patients (Ritschel et al., 2014), and acute and sustained IL-6 elevation was associated with larger final infarct size, more microvascular obstruction, lower left ventricular ejection fraction and adverse remodelling and events (Groot et al., 2019; Scărlătescu et al., 2022; Tiller et al., 2022; Tøllefsen et al., 2021). A meta-analysis confirmed higher IL-6 in patients with more severe acute coronary syndromes and in those who experienced major adverse cardiovascular events (Yang et al., 2021), and IL-6 has been proposed as a marker of myocardial necrosis in patients undergoing PCI (Bouzidi and Gamra, 2023). Mechanistically, IL-6 released by plaque macrophages, activated platelet–monocyte complexes and ischaemic cardiomyocytes activates the endothelium, up-regulates adhesion molecules and tissue factor, promotes leukocyte recruitment and microvascular obstruction, and thereby amplifies reperfusion injury and infarct expansion (Frangogiannis, 2014; Montecucco et al., 2016; Prabhu and Frangogiannis, 2016; Su et al., 2021). Peripheral IL-6, by contrast, integrates hepatic and adipose production and the influence of comorbidities and body composition (Wainstein et al., 2017), which may dilute the lesion-specific signal; this may explain why the systemic marker was less discriminative in our relatively small sample.

These findings have potential clinical and translational implications. Anti-inflammatory therapy targeting the IL-1β–IL-6 axis reduced recurrent cardiovascular events in patients with previous myocardial infarction and residual inflammation (Ridker et al., 2017), and a single dose of the IL-6 receptor antagonist tocilizumab attenuated the inflammatory response and PCI-related troponin T release in non-ST-elevation myocardial infarction (Kleveland et al., 2016) and increased myocardial salvage when given during PPCI in STEMI (Broch et al., 2021). Intracoronary IL-6 can be obtained during PPCI without additional procedural risk and, if confirmed in larger studies, might help to identify patients with a pronounced local inflammatory response who stand to benefit most from such therapies. It should be stressed, however, that the correlation observed here was weak ($r = 0.209$, corresponding to roughly 4% of shared variance), so intracoronary IL-6 alone is unlikely to serve as a stand-alone marker of infarct size; its value is more likely to lie in combination with clinical variables, necrosis biomarkers and imaging.

3.6 Strengths and limitations

This study has several limitations. It was conducted in a single centre with a sample size calculated for the detection of a modest correlation, which limits the precision of the estimates and precludes subgroup analyses. IL-6 was measured at a single time point in each compartment and the interval from symptom onset to sampling was not standardised, which is important because IL-6 kinetics are time-dependent; peripheral and intracoronary samples were also not obtained simultaneously. Intracoronary blood was aspirated proximal to the culprit lesion rather than from the lesion site, which may have attenuated the local signal. Peak hs-TnI depended on the clinical sampling schedule, infarct size was not confirmed by cardiac magnetic resonance or echocardiographic assessment of left ventricular function, and C-reactive protein and other inflammatory markers were not analysed. Potential confounders, including age, sex, the high prevalence of hypertension and diabetes, Killip class, ischaemic time, culprit vessel, thrombus burden and post-procedural Thrombolysis in Myocardial Infarction flow, were not adjusted for in multivariable models, and clinical outcomes were not analysed. The strengths of the study include its prospective design with paired sampling of both compartments in the same patients, consecutive enrolment of a well-defined PPCI population and the provision of data from a Southeast Asian population that is under-represented in the literature. Larger multicentre studies with standardised distal intracoronary sampling, serial measurements of IL-6 and troponin, imaging-based quantification of infarct size and microvascular obstruction, and follow-up for major adverse cardiovascular events are warranted to establish the prognostic and therapeutic relevance of local coronary inflammation in STEMI.

4. CONCLUSION

In STEMI patients undergoing PPCI, IL-6 concentrations in the culprit coronary artery differ significantly from those in peripheral blood. Intracoronary IL-6 was higher in patients with a greater degree of myocardial injury and correlated positively, although weakly, with peak hs-TnI, whereas peripheral IL-6 did not. Local coronary inflammation therefore appears to reflect the severity of myocardial injury more closely than systemic inflammation, and intracoronary IL-6 merits further evaluation as a lesion-specific inflammatory biomarker in STEMI. Future multicentre studies with standardised distal intracoronary sampling, serial cytokine and troponin measurements, imaging-based infarct quantification and clinical follow-up are recommended to define its prognostic value and its potential role in selecting patients for targeted anti-inflammatory therapy.

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AUTHOR CONTRIBUTIONS

Aulia Fadhilah Tasruddin: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing—Original Draft, Final Approval.

Abdul Hakim Alkatiri: Conceptualization, Methodology, Resources (provision of study patients), Formal Analysis, Supervision, Writing—Review & Editing, Final Approval.

Az Hafid Nashar: Conceptualization, Methodology, Resources (provision of study patients), Formal Analysis, Project Administration, Writing—Review & Editing, Final Approval.

Muzakkir Amir: Conceptualization, Methodology, Resources (provision of study patients), Writing—Review & Editing, Final Approval.

Khalid Saleh: Formal Analysis, Project Administration, Writing—Review & Editing, Final Approval.

Andi Alfian Zainuddin: Formal Analysis (statistical expertise), Validation, Writing—Review & Editing, Final Approval.

All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Statement

This study involving human subjects was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin / Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia (approval No. 598/UN4.6.4.5.31/PP36/2023, dated 29 August 2023; extension No. 142/UN4.6.4.5.31/PP36/2025, dated 28 February 2025; protocol No. UH23070470). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants or their legal representatives.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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