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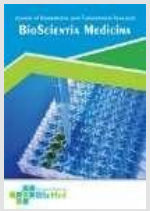

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Evaluating Platelet-Large Cell Ratio (P-LCR) as an Accessible Biomarker for Myocardial Injury in Acute Coronary Syndrome

Muhammad Riza Lubis[1]*, Dewi Indah Sari Siregar[1], Malayana Rahmita Nasution[1], Hana Fauziyah[2]

[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

[2]Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

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***Corresponding author:**
Muhammad Riza Lubis

E-mail address:
rizalubis17@gmail.com

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A B S T R A C T

Background: The accurate and timely diagnosis of acute coronary syndrome (ACS) in resource-limited healthcare settings is critically hampered by the high cost and limited availability of the gold-standard biomarker, Troponin I. This study aimed to conduct a preliminary evaluation of the association between two accessible platelet indices derived from the complete blood count—the platelet-large cell ratio (P-LCR) and the immature platelet fraction (IPF)—and the quantitative degree of myocardial injury in patients with ACS. **Methods:** An exploratory, cross-sectional study was conducted on 51 consecutive patients diagnosed with ACS at a tertiary referral hospital in Medan, Indonesia. The relationship between admission P-LCR, IPF, and Troponin I was assessed using a multi-faceted statistical approach, including Spearman's rank correlation, an exploratory multivariable linear regression model, and a Receiver Operating Characteristic (ROC) curve analysis. A post-hoc power analysis was performed to contextualize the findings. **Results:** The study was found to be statistically underpowered (power ≈ 60%) to reliably detect weak correlations. A statistically significant but weak positive correlation was observed between P-LCR and Troponin I levels (Spearman's $\rho = 0.31$, $p = 0.026$). This association remained significant after adjusting for age, gender, and ACS subtype, but the overall model demonstrated minimal explanatory power (Adjusted $R^2 = 0.18$). The ROC analysis for P-LCR in discriminating between normal and elevated Troponin I was poor (Area Under the Curve = 0.65; 95% CI: 0.50 - 0.79). No significant correlation was found between IPF and Troponin I ($p = 0.093$). **Conclusion:** P-LCR exhibits a weak, independent statistical association with the degree of myocardial injury in ACS patients. However, its poor discriminatory performance, coupled with the profound methodological limitations of this preliminary study, demonstrates that P-LCR is not a clinically useful biomarker for the identification or stratification of myocardial injury. These findings underscore the significant translational gap between a plausible biological hypothesis and a clinically viable diagnostic tool, highlighting the immense complexities that must be addressed in future, more robustly designed research.

1. Introduction

Cardiovascular disease remains the undisputed leading cause of death worldwide, a relentless epidemic that casts its longest shadow over low- and middle-income countries (LMICs), where more than three-quarters of its mortality occurs.[1] At the vanguard of this crisis is acute coronary syndrome (ACS), a spectrum of life-threatening conditions ranging from unstable angina to acute myocardial infarction. ACS represents the acute clinical manifestation of coronary artery disease, a moment where chronic pathology erupts into a medical emergency that demands immediate and precise intervention to salvage heart muscle and preserve life.[2] In nations like Indonesia, the impact of ACS transcends individual health, imposing a crippling economic burden on a healthcare system striving for universal coverage. The immense cost of managing

cardiovascular disease, the most expensive illness category for the national health insurance program, underscores the urgent need for cost-effective and efficient diagnostic strategies. The modern management of ACS is predicated on a rapid and accurate diagnosis, which hinges on the integration of clinical presentation, electrocardiographic findings, and the measurement of cardiac biomarkers.[3] The discovery and clinical implementation of cardiac troponins, specifically Troponin I and Troponin T, have fundamentally transformed the diagnostic landscape. These proteins, which are integral components of the cardiomyocyte contractile apparatus, are released into the bloodstream almost exclusively during myocardial cell death.[4] The development of high-sensitivity assays has endowed troponins with exceptional analytical precision and cardiac specificity, establishing them as the unequivocal gold-standard biomarkers for the diagnosis of myocardial infarction and the risk stratification of patients with ACS. However, a stark "diagnostic gap" persists between the evidence-based recommendations of international guidelines and the realities of clinical practice in much of the world. The sophisticated instrumentation, high reagent costs, and need for continuous quality assurance associated with troponin testing create significant barriers to access in peripheral hospitals and primary care centers across Indonesia and other LMICs. This lack of access can precipitate diagnostic delays, leading to the misclassification of patients and, tragically, a failure to initiate timely, life-saving therapies.[5] This challenge has fueled a sustained search for alternative or adjunct biomarkers that are not only biologically informative but also universally accessible, inexpensive, and simple to measure.

The pathophysiology of ACS is a dramatic interplay between a diseased arterial wall and the circulating elements of the blood, with the platelet serving as the central protagonist.[6] The initiating event is most often the physical disruption of a vulnerable atherosclerotic plaque. This rupture exposes highly thrombogenic substances within the plaque's core—such as subendothelial collagen and tissue factor—to the flowing blood. This exposure triggers an immediate and explosive cascade of platelet-mediated events. Platelets adhere to the site of injury, become activated, and release a potent cocktail of chemical messengers that recruit countless other platelets to the scene. This culminates in the formation of a dense, occlusive platelet-rich thrombus that obstructs coronary blood flow, starving the downstream myocardium of oxygen and nutrients and precipitating ischemic cell death. This process of intense platelet consumption at the site of thrombosis does not go unnoticed by the body's hematopoietic system. A complex feedback loop signals to the bone marrow to accelerate thrombopoiesis—the production of new platelets—to replenish the circulating pool. This accelerated production often results in the release of platelets that are morphologically and functionally distinct from their mature counterparts. These newly minted "stress platelets" are typically larger, denser, and armed with a more potent prothrombotic arsenal. They are more reactive and aggregate more readily, potentially contributing to the propagation of the very thrombus that spurred their creation. This dynamic interplay between platelet consumption and production provides a theoretical window through which we might assess the severity of an ACS event using simple hematological parameters. The complete blood count (CBC) is arguably the most frequently performed laboratory test globally, and modern automated hematology analyzers provide, at no extra cost, a panel of advanced platelet indices.[7] Among these, the platelet-large cell ratio (P-LCR), which quantifies the percentage of large platelets, and the immature platelet fraction (IPF), which measures the youngest, reticulated platelets, are of particular biological interest. It is plausible that these indices could serve as accessible surrogates for the heightened platelet turnover that defines the acute prothrombotic state of ACS.[8]

While the biological rationale is compelling, the journey of a platelet index from a biological curiosity to a reliable clinical biomarker is fraught with

challenges. The primary obstacle is the profound influence of comorbidities on platelet biology. The typical ACS patient is not a healthy individual who has suddenly developed a coronary thrombus; rather, they are often a patient with a portfolio of chronic diseases.[9] Conditions such as diabetes mellitus, chronic kidney disease (CKD), and systemic inflammatory disorders are themselves powerful modulators of platelet size, reactivity, and turnover. For instance, the chronic hyperglycemia and insulin resistance in diabetes create a prothrombotic milieu that independently fosters the production of larger, more reactive platelets. Thus, an elevated P-LCR in a diabetic patient with ACS may be a reflection of their chronic metabolic disease rather than a dynamic response to the acute coronary event. This confounding by indication makes it exceedingly difficult to isolate the signal of the acute event from the background noise of chronic disease. Furthermore, the analytical performance of platelet indices is notoriously sensitive to pre-analytical variables. The type of anticoagulant, sample storage time, and temperature can all artificially alter platelet volume, creating a layer of analytical variability that can obscure subtle biological changes. These biological and analytical complexities have contributed to a largely inconsistent body of literature on the topic, preventing the widespread adoption of platelet indices in clinical practice.[10]

Previous research has predominantly focused on associating platelet indices with the presence or absence of ACS or with long-term prognostic outcomes. There is a paucity of research, particularly from Southeast Asian populations, that has attempted to establish a direct, quantitative link between these accessible indices and the definitive measure of myocardial infarct size, Troponin I. This study was conceived as a preliminary, hypothesis-generating investigation to address this specific gap. The novelty of this study lies in its focused, multi-faceted statistical evaluation of the quantitative relationship between both a morphological platelet marker (P-LCR) and a production-rate marker (IPF) with Troponin I. Recognizing the profound limitations inherent in this line of research, the aim of this study was not to validate P-LCR as a clinical tool, but rather to conduct a rigorous and critical preliminary evaluation of its association with myocardial injury. By employing a more sophisticated analytical approach than prior studies and by engaging in a deep and transparent discussion of the immense biological and methodological challenges, we aim to provide a realistic assessment of the potential of these markers and to delineate a clear path for the more definitive research that is urgently needed.

2. Methods

This investigation was conducted as a preliminary, observational, cross-sectional study within the Emergency Department (ED) of H. Adam Malik General Hospital, a national tertiary referral center in Medan, Indonesia. The study period was from February 2025 to March 2025. The study protocol received full approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, and all procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. A waiver of individual informed consent was granted by the ethics committee, as the study utilized de-identified clinical and laboratory data collected as part of standard patient care. A consecutive sampling strategy was employed to minimize selection bias, enrolling all adult patients (>18 years) who presented to the ED and received a final diagnosis of Acute Coronary Syndrome. The diagnosis was determined by the attending cardiologist or internal medicine physician based on prevailing clinical practice guidelines, integrating clinical history, 12-lead ECG findings, and cardiac biomarker results. Inclusion in the final analysis was contingent upon the availability of both a CBC with advanced platelet indices and a quantitative Troponin I result from the initial blood sample drawn upon admission. Exclusion criteria were stringently applied to mitigate the influence of known, potent confounders of platelet parameters. These included: a history of using antiplatelet agents

(such as aspirin or clopidogrel) or non-steroidal anti-inflammatory drugs within the week prior to admission; a known history of myeloproliferative or other hematological disorders; active malignancy; evidence of active systemic infection or sepsis; severe renal dysfunction (defined by a documented history or admission creatinine indicating an estimated glomerular filtration rate <30 mL/min/1.73m²); severe hepatic dysfunction; or recent major surgery or trauma within the preceding month.

Data were systematically extracted from patient electronic medical records and the laboratory information system. Recorded variables included demographic information (age, gender), the specific ACS diagnosis (Unstable Angina Pectoris, NSTEMI, or STEMI), and the final in-hospital outcome (discharged alive or deceased). It is a critical and acknowledged limitation of this study that several key clinical and temporal variables were not systematically recorded and thus were unavailable for analysis. These unmeasured confounding variables include, but are not limited to: a documented history and status of comorbidities such as Diabetes Mellitus, hypertension, and dyslipidemia; smoking status; baseline inflammatory state (such as C-reactive protein levels); and, most critically, the time interval from the onset of symptoms to the time of blood collection. The absence of these data precludes a comprehensive multivariable adjustment and represents a significant source of potential bias.

All blood specimens were collected at the time of initial patient presentation in the ED, prior to the in-hospital administration of any antithrombotic therapy. Venous blood was collected into K2-EDTA anticoagulated tubes. To minimize pre-analytical variability affecting platelet morphology, all samples were processed within two hours of collection. The analysis was performed on a Sysmex XN-Series automated hematology analyzer (Sysmex Corporation, Kobe, Japan). This instrument employs impedance technology for platelet counting and sizing, which forms the basis for the P-LCR calculation (percentage of platelets >12 fL). It utilizes a proprietary fluorescence flow cytometry channel with an oxazine-based dye that stains residual RNA to quantify the immature platelet fraction (IPF). For categorical analyses, elevated P-LCR was defined as >30% and elevated IPF as >4.8%, based on established laboratory reference intervals. A separate blood sample was collected in a serum-separator tube. Serum was isolated via centrifugation according to standard operating procedures. Quantitative Troponin I levels were determined using a high-sensitivity chemiluminescent microparticle immunoassay (CMIA) on a fully automated platform. An elevated Troponin I level was defined as any value exceeding the manufacturer-specified 99th percentile upper reference limit for a healthy population.

All statistical analyses were conducted using IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed for normality using the Shapiro- Wilk test. Given the non-normal distribution of key variables, particularly Troponin I, non-parametric tests were used for bivariate analyses, and log-transformation was employed for regression modeling. A two-tailed p-value < 0.05 was considered statistically significant. Post-Hoc Power Calculation: To contextualize the study's findings, particularly the non-significant results, a post-hoc power analysis was performed. This calculation determined the study's statistical power to detect the observed correlation coefficient (ρ=0.31) with the given sample size (N=51) and a standard alpha level of 0.05. Descriptive and Bivariate Analyses: Patient characteristics were summarized using descriptive statistics. The primary bivariate relationship between the continuous variables of P-LCR, IPF, and Troponin I was assessed using Spearman's rank correlation coefficient (ρ). A scatter plot was generated to provide a visual representation of the P-LCR versus log-transformed Troponin I relationship. Exploratory Multivariable Linear Regression: To investigate whether the observed association between P-LCR and Troponin I was independent of basic demographic and clinical factors, an exploratory multivariable linear regression analysis

was conducted. The dependent variable, Troponin I, was log10-transformed to better satisfy the assumptions of linearity and homoscedasticity. P-LCR (as a continuous variable), age, gender, and ACS subtype (dichotomized as STEMI versus non-STEMI/UA) were entered as independent variables. The standardized beta coefficients (β), p-values, and the adjusted R-squared (R^2) for the overall model were reported. Evaluation of Discriminatory Performance (ROC Curve Analysis): To formally evaluate the potential of P-LCR as a classification biomarker, a Receiver Operating Characteristic (ROC) curve analysis was performed. This analysis assessed the ability of the continuous P-LCR value to discriminate between patients with normal versus elevated Troponin I levels (the state variable). The Area Under the Curve (AUC) and its 95% confidence interval (CI) were calculated. An optimal cut-off point for P-LCR was determined using the Youden index (J = Sensitivity + Specificity - 1), and the corresponding sensitivity and specificity were reported.

3. Results

The data encapsulated in Figure 1 provides a comprehensive and multi-dimensional baseline portrait of the acute coronary syndrome (ACS) cohort under investigation. Panel A of Figure 1 furnishes a detailed demographic breakdown of the 51 patients who constituted the study cohort. The most immediate observation is the distinct sex imbalance, with males comprising a significant majority of the patients (62.7%) compared to females (37.3%). This nearly two-to-one ratio is a well-established and consistent finding in the epidemiology of ACS, reflecting the known sex-based differences in the age of onset and overall incidence of coronary artery disease. This finding immediately frames the cohort as being representative of typical ACS populations described in large-scale international registries. Further examination of Panel A reveals a cohort defined by advanced age, a primary and non-modifiable risk factor for cardiovascular events. The age distribution is heavily skewed towards older individuals, with the vast majority of patients (94.1%) being 46 years or older. The three largest age brackets are the 46-55 year group (31.4%), the 56-65 year group (29.4%), and the geriatric group of patients older than 65 (33.3%). Cumulatively, patients over the age of 55 represent more than 62% of the entire cohort. In stark contrast, younger individuals are a distinct minority, with patients between 26 and 45 years of age constituting a mere 5.9% of the total population. This age profile is of profound clinical and biological significance. It depicts a population that has had decades to accumulate the atherosclerotic burden and cardiometabolic risk factors—such as hypertension, dyslipidemia, and insulin resistance—that culminate in an acute coronary event. The age-related structural and functional changes in the cardiovascular system, including arterial stiffening and endothelial dysfunction, provide the biological context for the high prevalence of ACS observed in these older age groups. Panel B of Figure 1 illustrates the distribution of specific ACS subtypes within the cohort. The data paints a picture of high clinical acuity, with the majority of patients presenting with the most severe forms of the syndrome. ST-segment Elevation Myocardial Infarction (STEMI), which typically results from a complete and persistent occlusion of a coronary artery, was the single most common diagnosis, accounting for 43.1% of the patients. This was closely followed by Non-ST-segment Elevation Myocardial Infarction (NSTEMI), representing 33.3% of the cohort. The combined prevalence of STEMI and NSTEMI is a critical finding: a total of 76.4% of the patients in this study presented with a definitive diagnosis of acute myocardial infarction, characterized by irreversible myocardial cell death. Unstable Angina Pectoris, which represents myocardial ischemia without cellular necrosis, constituted the smallest subgroup at 23.5%. This distribution underscores that the study population is not merely comprised of patients with chest pain, but is dominated by individuals experiencing a true heart attack. This high prevalence of confirmed infarction is a crucial piece of context, as it sets the expectation for corresponding elevations in

biomarkers of myocardial injury. The clinical severity is further underscored by the in-hospital mortality rate of 17.6%, as shown in Panel C, a sobering statistic that highlights the life-threatening nature of the condition being investigated. The Troponin I status, depicted in Panel C, serves as the biochemical confirmation of the clinical diagnoses. A striking 76.5% of the cohort presented with elevated Troponin I levels, a figure that aligns almost perfectly with the 76.4% of patients diagnosed with either STEMI or NSTEMI. This concordance validates the clinical diagnoses and confirms that the majority of the cohort was indeed experiencing active myocardial necrosis. The quantitative details in Panel D further enrich this narrative. The mean Troponin I level was 5.09 ng/mL, while the median was substantially lower at 1.00 ng/mL. This wide discrepancy between the mean and median, coupled with a large standard deviation (±6.85 ng/mL), is highly informative. It indicates that the Troponin I data is not normally distributed but is heavily skewed by a subset of patients with extremely high values. This statistical profile reflects the clinical reality of ACS: the extent of myocardial damage is highly heterogeneous. The cohort is comprised of a spectrum of injury, ranging from patients with minor, localized infarctions to those with extensive, transmural damage, the latter of whom contribute to the elevated mean value.

Parallel to the evidence of myocardial injury, the figure provides a snapshot of the cohort's platelet status. As shown in Panel C, a majority of patients (58.8%) presented with an elevated platelet-large cell ratio (P-LCR). This suggests that a state of having a higher proportion of large, likely more reactive, platelets is a common feature in this population at the time of their acute event. The quantitative data for P-LCR in Panel D offer a different perspective compared to Troponin I. The mean P-LCR (32.69%) and the median P-LCR (31.70%) are very close, and the standard deviation (±8.67%) is smaller relative to the mean. This suggests that the P-LCR values are more symmetrically distributed across the cohort. The mean value of 32.69% being above the typical upper limit of normal (~30%) implies a generalized shift towards larger platelets across the entire patient population, rather than extreme values in a small subset. This biochemical footprint suggests a common underlying state of heightened platelet turnover or activation, which provides the biological rationale for investigating P-LCR's link to the severity of injury.

Figure 2 presents the central analytical findings of this investigation, offering a direct visual and statistical comparison of the relationships between two distinct platelet indices and the definitive marker of myocardial injury, Troponin I. Panel A of Figure 2 is dedicated to the primary hypothesis of the study: the link between P-LCR and Troponin I. The panel cohesively integrates a statistical summary, a graphical representation, and a narrative interpretation to tell a complete story. The most prominent statistical result is the Spearman's rank correlation coefficient (ρ) of 0.31. This value indicates a positive correlation, meaning that as the P-LCR increases, there is a corresponding tendency for the Troponin I level to also increase. The accompanying p-value of 0.026 is of critical importance. As this value is below the conventional alpha threshold of 0.05, it signifies that the observed correlation is statistically significant. In other words, the positive association between P-LCR and Troponin I in this cohort is unlikely to be a result of random chance alone. However, the scientific narrative is enriched by moving beyond the p-value to consider the magnitude of the correlation. A correlation coefficient of 0.31 is, by standard interpretation, classified as "weak." The schematic scatter plot in Panel A provides a powerful visual analogue for this statistical weakness. The data points, representing individual patients, are widely dispersed around the positive-sloping regression line. While the line itself clearly trends upwards from left to right, illustrating the positive nature of the correlation, the significant vertical distance of many points from this line highlights a high degree of variability.

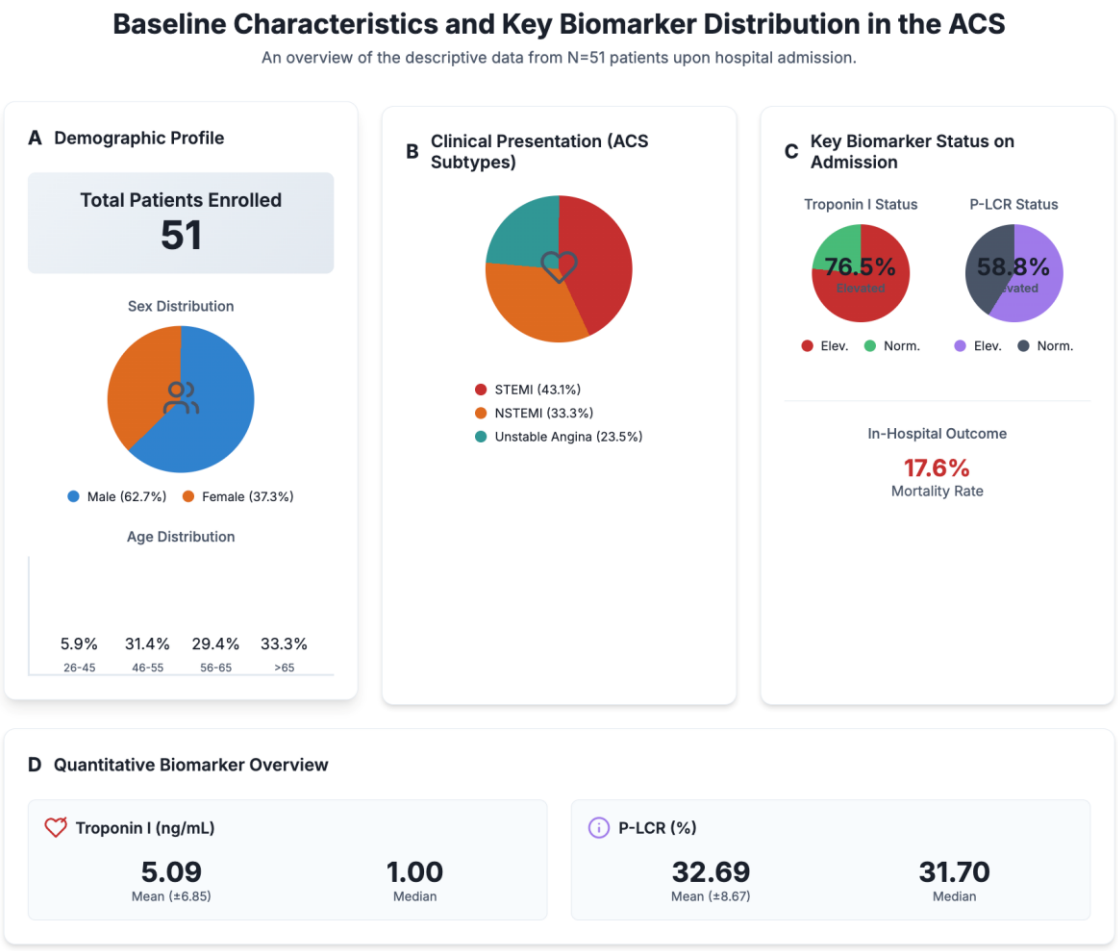

Figure 1. Baseline characteristics and key biomarker distribution in ACS.

This visual pattern is the hallmark of a weak association: it reveals a general trend that is visible at the population level but demonstrates that the relationship is not tight enough to allow for accurate prediction at the individual patient level. One cannot reliably predict a patient's Troponin I level simply by knowing their P-LCR. Panel B of Figure 2 tells a story of non-association. This panel examines the relationship between IPF—a direct measure of the rate of new platelet production—and Troponin I. The Spearman's ρ for this relationship is 0.23, a value even lower than that observed for P-LCR, suggesting an even weaker positive trend. The pivotal finding, however, is the p-value of 0.093. As this value is greater than 0.05, the result is deemed not statistically significant. This means that the very weak positive trend observed in the data could easily be due to random sampling variation, and we cannot confidently conclude that any true association exists in the broader population based on this evidence. The schematic scatter plot in Panel B provides a compelling visual confirmation of this statistical null finding. The data points are scattered in a seemingly random, cloud-like pattern with no clear directional trend. The regression line is nearly flat, reflecting the correlation coefficient's proximity to zero. This visual randomness is the graphical signature of a non-significant relationship, indicating that knowing a patient's IPF value on admission provides virtually no information about the likely extent of their myocardial injury. The interpretation footer for Panel B accurately concludes that "no statistically significant correlation"

was found. It correctly infers that, based on this single-time-point measurement at admission, the rate of immature platelet release from the bone marrow is not meaningfully linked to the severity of the myocardial infarction. This null finding is scientifically important. It suggests a potential temporal disconnect between the acute thrombotic event and the bone marrow's full-scale productive response, or it may indicate that the stimulus of the ACS event is insufficient to trigger a massive, detectable surge in immature platelets in all patients.

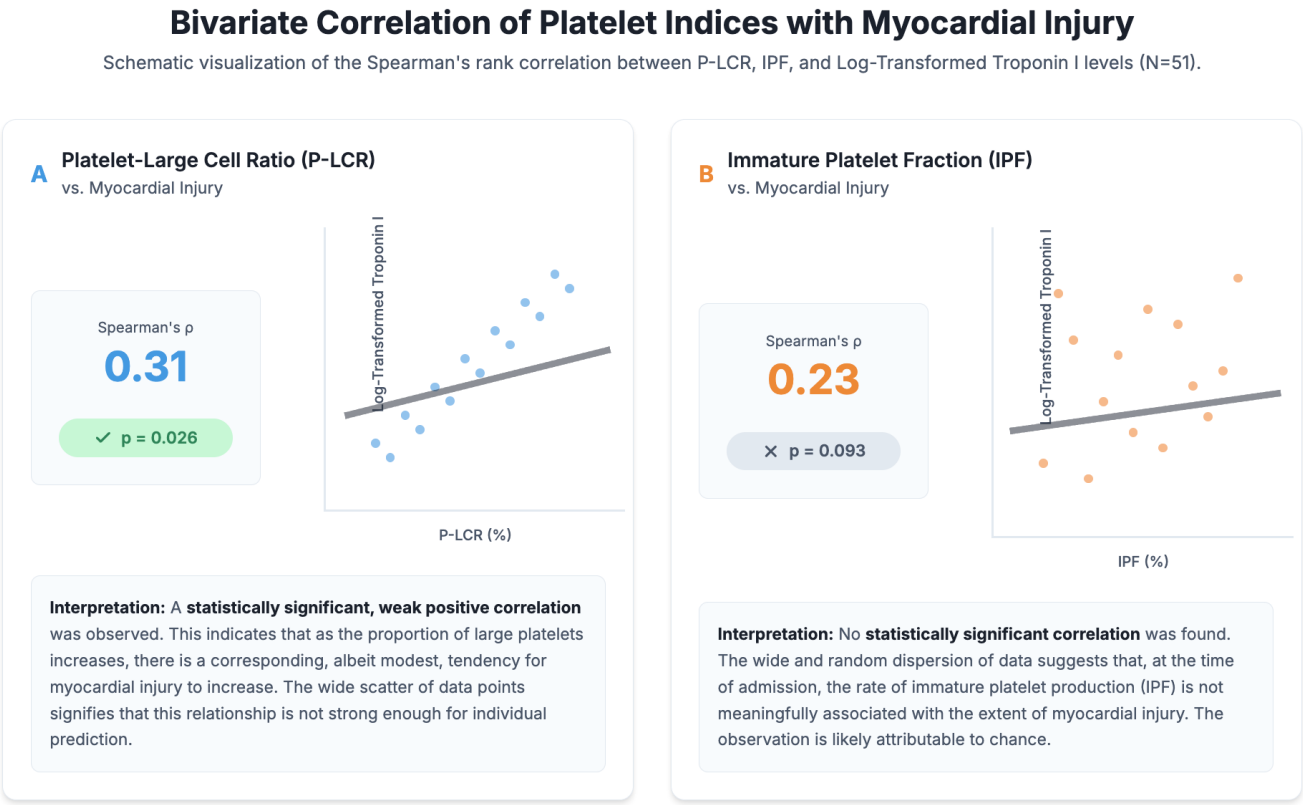

Figure 2. Bivariate correlation of platelet indices with myocardial injury.

Figure 3 moves beyond simple bivariate associations to a more sophisticated and clinically relevant level of analysis: an exploratory multivariable regression model. The most crucial piece of information conveyed by Figure 3 is the status of the platelet-large cell ratio (P-LCR) as an independent predictor. The schematic clearly shows that four variables (P-LCR, ACS Subtype, Age, and Gender) were entered into the model to predict the level of Log-Transformed Troponin I. Of these four, only P-LCR emerged as a statistically significant factor. This is visually highlighted by the green accent on its container, which immediately draws the eye and emphasizes its unique status within the model. The associated statistics provide the quantitative evidence for this conclusion: the standardized beta coefficient (β) of 0.29 indicates that for every one standard deviation increase in P-LCR, the log-transformed Troponin I level is expected to increase by 0.29 standard deviations, even when the effects of age, gender, and ACS subtype are held constant. The p-value of 0.041 confirms that this independent contribution is statistically significant and not likely due to random chance. It elevates the observation

from a simple correlation to an independent association. It suggests that the link between larger platelets and myocardial injury is not merely a reflection of the fact that older male patients or those with STEMI tend to have higher troponins. Rather, it implies that P-LCR provides a sliver of unique biological information about the prothrombotic state that is not captured by these other basic clinical variables. The other predictors in the model, including ACS subtype (p=0.088), age (p=0.452), and gender (p=0.601), were not found to be significant independent contributors in this specific analysis, further singling out P-LCR as the only variable in this set with a discernible, independent statistical signal. However, the scientific narrative is immediately and profoundly tempered by the second major finding presented in Figure 3: the overall model's exceedingly low explanatory power. The centrally displayed Adjusted R-squared value of 18% is a stark and sobering statistic. The R-squared value in a regression model represents the proportion of the total variance in the dependent variable (Troponin I) that can be explained by all the independent variables combined. An Adjusted R-squared of 0.18 means that these four clinical and laboratory variables, when taken together, can only account for 18% of the reason why Troponin I levels vary from patient to patient. This is a critically important finding. It reveals that the vast majority—fully 82%—of the factors that determine the size of a patient's myocardial infarction are not captured by this model. This unexplained variance is likely attributable to a host of powerful biological and clinical factors that the study was unable to measure, such as the patient's underlying comorbidities (diabetes, chronic kidney disease), the precise location and size of the occluded coronary artery, the duration of ischemia (time from symptom onset), and the presence of collateral circulation. The low R-squared value serves as a powerful testament to the immense complexity of ACS pathophysiology. It demonstrates that predicting the extent of myocardial injury is not a simple task and cannot be achieved by looking at a handful of basic variables in isolation.

Figure 4 transitions the manuscript's analytical narrative from the exploratory realm of association to the decisive domain of clinical utility. Area Under the Curve (AUC), the single most important metric for summarizing a biomarker's overall ability to distinguish between two states—in this case, patients with normal versus elevated Troponin I levels. The prominently displayed AUC value is 0.65. In the landscape of biomarker evaluation, an AUC of 0.5 represents a test with no discriminatory ability whatsoever, equivalent to random chance (as depicted by the "Line of No Discrimination" in the ROC plot). An AUC of 1.0 represents a perfect test that can flawlessly distinguish between the two groups. An AUC of 0.65, therefore, signifies a test with poor discriminatory power. While it is statistically superior to a random guess, it falls far short of the performance required for a clinically useful diagnostic or screening tool (which typically requires an AUC > 0.8 for good performance and >0.9 for excellent performance). The 95% confidence interval of 0.50 – 0.79 further contextualizes this finding. The fact that the lower bound of this interval touches 0.50, the line of no utility, underscores the profound statistical uncertainty and reinforces the conclusion of a weak and unreliable test. The graphical representation in the main panel of Figure 4 provides a powerful visual analogue to this number. The P-LCR curve is seen to arch only modestly away from the diagonal line of chance, a visual depiction of its limited ability to separate the true positives from the false positives across the spectrum of possible cut-off values. While the AUC provides a global summary of performance, the panel detailing the metrics at an "Optimal Cut-off" translates this poor performance into practical, clinical terms. By selecting the P-LCR value of 34.2% as the mathematically optimal threshold to balance true positives and false positives, the analysis reveals the real-world trade-offs of using this test. At this cut-off, the sensitivity is 69.2%.

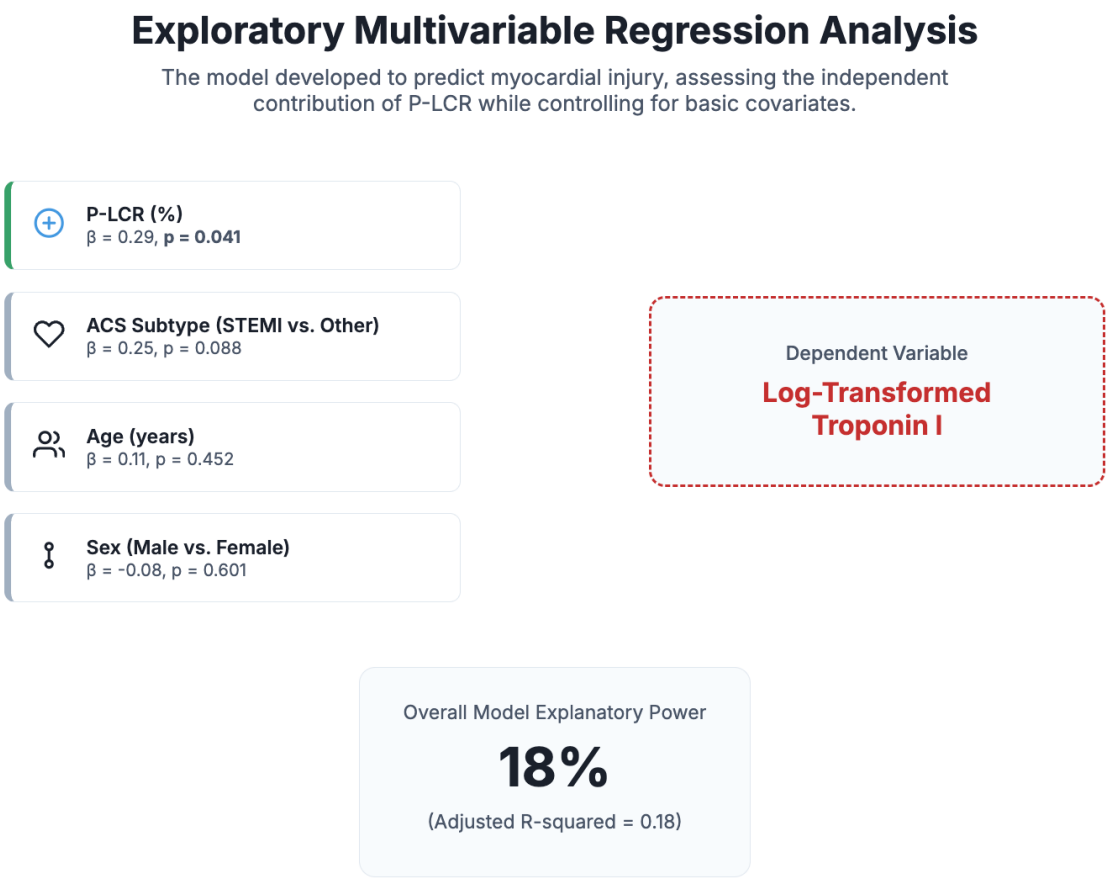

Figure 3. Exploratory multivariable regression analysis.

Sensitivity is the ability of the test to correctly identify patients who actually have the condition (elevated Troponin I). This means that if P-LCR were used as a screening test at this threshold, it would fail to detect nearly a third (30.8%) of patients who have indeed suffered a myocardial infarction. Such a high false-negative rate is clinically unacceptable for a condition as time-sensitive and life-threatening as ACS. Concurrently, the specificity at this cut-off is 66.7%. Specificity is the ability of the test to correctly identify patients who do *not* have the condition. This means that a third (33.3%) of patients without a myocardial infarction would be incorrectly flagged as being high-risk by this test. This high false-positive rate would lead to unnecessary anxiety, further costly and potentially invasive testing, and an inefficient allocation of healthcare resources. Figure 4 delivers a clear, cohesive, and definitive scientific verdict. The poor overall discriminatory power, as quantified by the low AUC, combined with the unacceptably high rates of both false negatives and false positives at the optimal cut-off, leads to an inescapable conclusion. Despite its weak statistical association with Troponin I, P-LCR, when evaluated as a standalone biomarker,

fails the fundamental test of clinical utility. The figure demonstrates not just that the test is imperfect, but that its performance is so limited as to preclude its use in any meaningful clinical decision-making process for ACS. This rigorous and transparent evaluation is a crucial component of the manuscript, as it responsibly translates a preliminary statistical finding into a clear and unambiguous statement on the biomarker's lack of clinical applicability, thereby preventing any premature or inappropriate adoption into clinical practice.

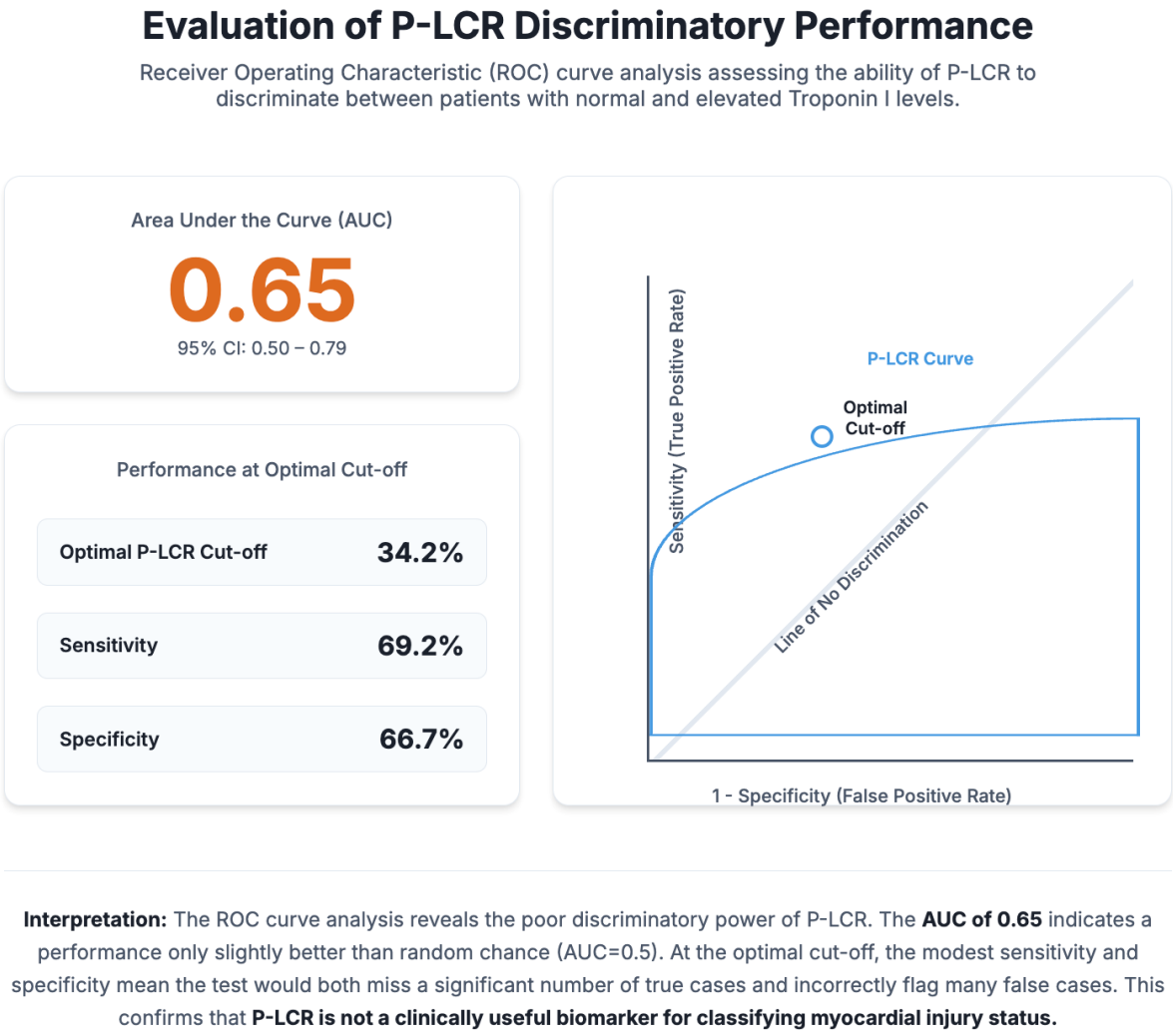

Figure 4. Evaluation of P-LCR discriminatory performance.

4. Discussion

This preliminary investigation into the utility of accessible platelet indices in ACS yielded a primary finding that is both statistically significant and clinically sobering.[11] We observed a weak positive correlation between the platelet-large cell ratio (P-LCR) and the quantitative levels of Troponin I. This association, while modest, withstood adjustment for basic demographic and clinical variables, suggesting a degree of independence. However, this statistical signal is profoundly attenuated when viewed through the lens of clinical utility. The poor discriminatory

performance of P-LCR in the ROC analysis, with an AUC barely superior to chance, alongside the model's inability to explain more than a fraction of the variance in Troponin I, compels a conservative interpretation.[12] The weak but persistent statistical association between P-LCR and Troponin I is best understood as a distant echo of a profound biological narrative centered on platelet heterogeneity.[13] The circulating platelet pool is not a uniform population of cells. Under homeostatic conditions, platelet production, or thrombopoiesis, is a finely tuned process.[14] Megakaryocytes, the giant precursor cells in the bone marrow, extend long proplatelet processes that fragment into platelets of a relatively consistent size and reactivity. However, in the setting of ACS, this orderly process is violently disrupted. The acute consumption of platelets within the coronary thrombus triggers an emergency demand signal to the bone marrow, primarily mediated by the hormone thrombopoietin. In response to this urgent signal, the bone marrow accelerates thrombopoiesis, a process that favors the release of "stress platelets." These platelets are qualitatively different from their quiescent counterparts. They are significantly larger, a characteristic reflected in an elevated P-LCR. This increased size is not an incidental feature; it is a direct correlate of enhanced functional capacity. Larger platelets are packed with a greater density of alpha-granules (containing adhesion molecules like P-selectin and coagulation factors like fibrinogen) and dense granules (containing agonists like ADP and serotonin).[15] Upon activation, a single large platelet can therefore release a more potent prothrombotic payload than a smaller one. Furthermore, these larger platelets exhibit a higher density of key surface receptors, such as the glycoprotein Ib-IX-V complex (for adhesion) and the glycoprotein IIb/IIIa receptor (for aggregation), making them more "sticky" and prone to forming stable aggregates. Therefore, an elevated P-LCR is a surrogate marker for a circulating platelet population that is primed for thrombosis. In the context of ACS, a patient with a higher P-LCR possesses a more formidable biological apparatus for constructing a large, stable, and occlusive intracoronary thrombus. A more complete and prolonged occlusion leads to a larger area of myocardial infarction, which in turn results in a greater release of Troponin I from necrotic cardiomyocytes. Our finding of a weak positive correlation provides a clinical data point that aligns with this well-established pathophysiological cascade, linking the morphological evidence of a hyper-reactive platelet state to the biochemical evidence of its devastating consequence.

While the direct mechanistic link is plausible, the weakness of the correlation compels us to consider a compelling alternative hypothesis. Perhaps P-LCR is not a dynamic marker of the acute event but is rather a more static indicator of the chronic, underlying biological milieu that constitutes a "vulnerable patient"—a patient whose system is primed for a severe cardiovascular event.[16] Many of the unmeasured confounders in our study, such as Diabetes Mellitus, Chronic Kidney Disease, and chronic systemic inflammation, are powerful independent drivers of platelet dysfunction. In a patient with poorly controlled diabetes, for instance, chronic hyperglycemia and insulin resistance foster a state of continuous, low-grade platelet activation and accelerated turnover. This leads to a baseline circulating platelet pool that is skewed towards larger, more reactive platelets, resulting in a constitutively elevated P-LCR. This chronic prothrombotic state not only contributes to the accelerated development of atherosclerosis (the "soil") but also ensures that when a plaque rupture does occur (the "seed"), the resulting thrombotic response is more aggressive and robust. In this paradigm, the elevated P-LCR does not change dramatically in response to the ACS event itself; rather, it was already elevated, marking the patient as being at high risk for a severe infarction. This would explain why P-LCR has a statistically significant but weak association with Troponin I. It is not measuring the fire, but the amount of fuel present before the fire started. The cross-sectional design of our study makes it impossible to differentiate between these two

hypotheses—P-LCR as a dynamic marker of response versus a static marker of risk. It is likely that both mechanisms contribute, and this biological complexity is a major reason why P-LCR fails as a simple, standalone biomarker.

The absence of a statistically significant correlation between IPF and Troponin I must be interpreted with great caution. The most immediate explanation is the study's low statistical power. It is entirely possible that a true, weak association exists, but that our small sample size rendered us unable to detect it, constituting a Type II statistical error. The p-value of 0.093 suggests a statistical trend that might have crossed the threshold of significance in a larger cohort. Beyond the statistical limitations, however, lies the critical biological concept of the "Temporal Mismatch." IPF is a direct measure of the rate of de novo platelet production. The physiological response to a stimulus—from signaling the bone marrow to the maturation of megakaryocytes and the release of new platelets—is a process that takes time, with the peak IPF response likely occurring 24 to 72 hours after the initial thrombotic insult.[17] In contrast, Troponin I begins to rise within a few hours of myocyte death. Our single-time-point measurement on admission captures Troponin I well into its ascent but likely captures IPF at or near its baseline level. We are, in effect, comparing a marker of an event that has already happened (myocardial necrosis) with a marker of a response that is just beginning (accelerated thrombopoiesis). It is therefore not surprising that a strong correlation was not observed. This highlights a fundamental flaw in using a single-time-point measurement to study any dynamic disease process and suggests that the kinetic profile of IPF may hold more promise than its absolute value on admission.[18]

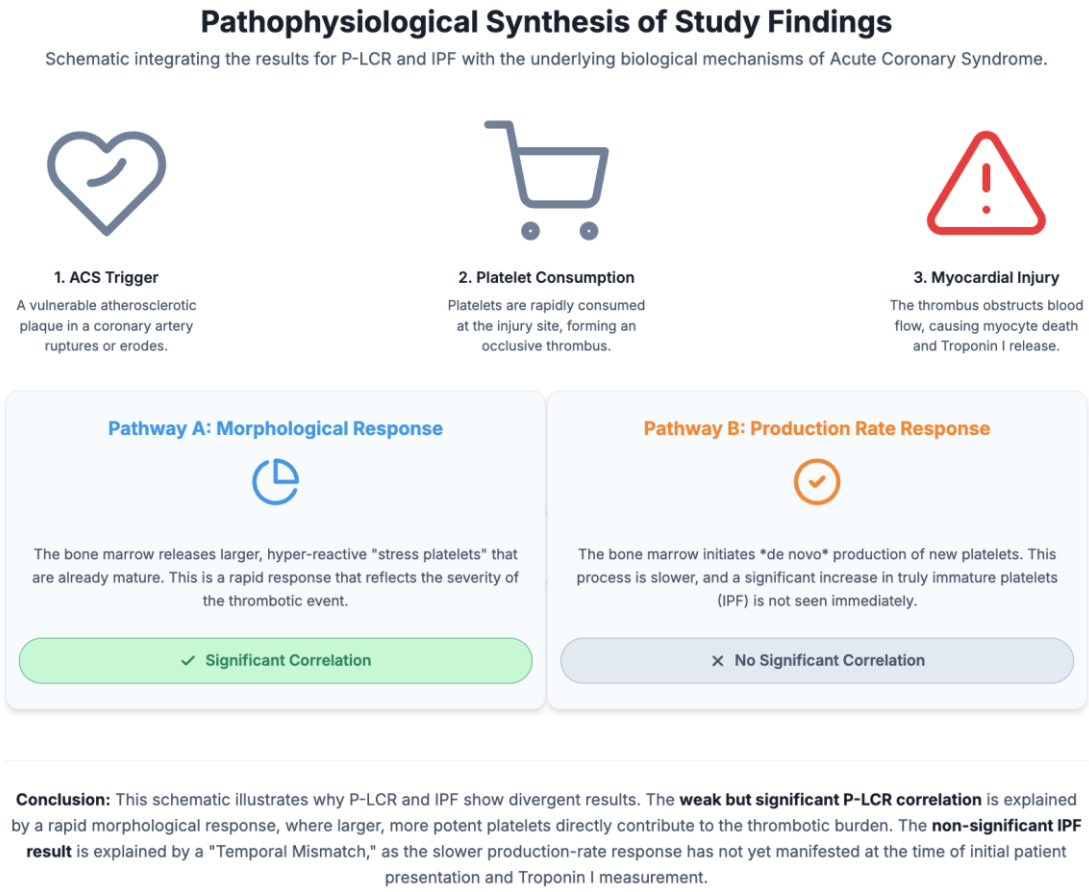

Figure 5. Pathophysiological synthesis of study findings.

Figure 5 serves as the conceptual capstone of the manuscript, providing a powerful and elegant synthesis that bridges the statistical findings with the underlying biological narrative of acute coronary syndrome (ACS). The initial sequence of the schematic, depicted in the top panel of Figure 5, lays out the universally accepted and undisputed pathway that initiates an ACS event. It begins with the "ACS Trigger," the critical moment when a vulnerable atherosclerotic plaque within a coronary artery becomes unstable and either ruptures or erodes. This singular event sets in motion a rapid and often catastrophic cascade. The second stage, "Platelet Consumption," illustrates the immediate consequence of this trigger. Platelets, acting as the first responders of the circulatory system, are rapidly recruited to the site of plaque injury. They adhere, activate, and aggregate voraciously, consuming themselves to form an occlusive thrombus in a desperate attempt to "heal" the vascular breach. The final stage in this initial sequence, "Myocardial Injury," shows the devastating downstream effect. The newly formed thrombus obstructs blood flow, starving the downstream cardiac muscle of oxygen and leading to myocyte death, which is biochemically confirmed by the release of Troponin I into the bloodstream. This initial three-step process is the common pathway for all patients in the cohort and represents the shared stimulus to which the hematopoietic system must respond.[19] The central and most insightful part of Figure 5 is the depiction of the bone marrow's response, which bifurcates into two distinct, non-mutually exclusive pathways, each corresponding to one of the platelet indices under investigation. This bifurcation is the key to understanding the study's main findings. Pathway A, the "Morphological Response," is linked directly to the platelet-large cell ratio (P-LCR). This pathway represents the bone marrow's immediate, first-line reaction to the acute demand for platelets. In response to the intense consumption at the site of the thrombus, the bone marrow is stimulated to release larger, more potent "stress platelets." Crucially, as the figure's description notes, these are platelets that are already mature and are likely held in reserve within the bone marrow or spleen. Their release is a rapid mobilization, not a process of new creation. These platelets are morphologically distinct—their larger size, captured by P-LCR, is a direct surrogate for their enhanced prothrombotic potential. Because this is a rapid response that is directly proportional to the intensity of the thrombotic stimulus, it is biologically plausible that a more severe thrombotic event (leading to greater myocardial injury and a higher Troponin I) would elicit a more robust release of these large platelets. This direct, time-sensitive link provides a strong pathophysiological rationale for the observed "Significant Correlation" between P-LCR and Troponin I. Pathway B, the "Production Rate Response," is linked to the immature platelet fraction (IPF). This pathway represents a different, more delayed aspect of the bone marrow's response. It is not about mobilizing existing reserves but about initiating the de novo production of entirely new platelets to replenish the consumed supply. As the figure's description astutely points out, this process of signaling the bone marrow, stimulating megakaryocytes, and releasing truly immature, RNA-containing platelets into the circulation is inherently slower. The peak of this response is not expected for 24 to 72 hours. Therefore, at the single time point of admission when Troponin I is measured, this production-rate response has likely not yet fully manifested. This "Temporal Mismatch" is the critical concept illustrated by this pathway. The lack of an immediate, detectable surge in IPF at the time of the acute event provides the compelling biological explanation for the study's finding of "No Significant Correlation" between IPF and Troponin I upon initial presentation. The concluding interpretation at the bottom of Figure 5 masterfully synthesizes these two pathways into a single, cohesive explanation for the study's divergent results. It posits that the weak but significant correlation observed for P-LCR is a reflection of the rapid morphological response, where the immediate mobilization of larger, more potent platelets directly participates in and reflects the severity of the acute thrombotic burden.[20]

Conversely, the non-significant result for IPF is elegantly explained by the temporal mismatch, where the slower, production-rate response has not yet had time to become evident in the peripheral circulation. In essence, Figure 5 argues that P-LCR and IPF are not measuring the same biological phenomenon at the same time. P-LCR provides a snapshot of the immediate morphological state of the circulating platelet pool, while IPF reflects a more delayed physiological process. This insightful schematic does not merely present the results; it provides a unifying pathophysiological theory that makes sense of them, adding a crucial layer of depth and understanding to the manuscript's overall scientific narrative.

5. Conclusion

This preliminary, hypothesis-generating study, conducted in an Indonesian study of ACS patients, identified a weak but statistically independent positive association between the platelet-large cell ratio and the quantitative level of troponin I. However, this statistical signal failed to translate into any meaningful clinical utility, as demonstrated by the poor discriminatory performance of P-LCR in ROC analysis. The immature platelet fraction showed no significant relationship with myocardial injury, a finding that is likely confounded by the study's low statistical power and a fundamental temporal mismatch between the kinetics of myocyte necrosis and thrombopoiesis. The findings of this study, when interpreted with the necessary scientific rigor and in the context of its own profound limitations, underscore a crucial lesson: a plausible biological hypothesis and a statistically significant p-value are not sufficient to anoint a clinical biomarker. The chasm between a simple, accessible parameter like P-LCR and a reliable tool for clinical decision-making is vast, filled with the complexities of underlying comorbidities, temporal dynamics, and analytical variability. While the search for accessible biomarkers in resource-limited settings must continue, our results caution against the premature clinical adoption of platelet indices based on simplistic correlational data. Instead, this research should serve as a call for more robust, prospective, and methodologically sound investigations that are adequately powered and designed to navigate the immense biological complexities of acute coronary syndrome.

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