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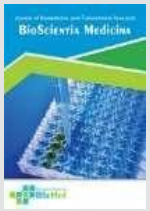

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Platelet-to-Lymphocyte Ratio as a Potential Diagnostic Marker for Acute Coronary Syndromes in Resource-Limited Settings: A Cross-Sectional Study from Single Center in Banten, Indonesia

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A B S T R A C T

Background: Acute coronary syndrome (ACS) poses a significant global health burden, particularly in resource-limited settings where access to advanced diagnostic tools is often constrained. The platelet-to-lymphocyte ratio (PLR), a simple and readily available marker from routine blood tests, has shown promise as a potential diagnostic tool for ACS. This study aimed to evaluate the diagnostic accuracy of PLR in identifying ACS patients in a resource-limited setting in Indonesia. **Methods:** A cross-sectional study was conducted at Hermina Periuk Hospital, Tangerang, Banten, Indonesia, between December 2020 and December 2022. Patients presenting to the Emergency Room with a diagnosis of ACS were included. PLR was calculated from complete blood count data, and cardiac troponin I (cTnI) served as the gold standard for ACS diagnosis. The diagnostic performance of PLR in predicting elevated cTnI levels was assessed. **Results:** Of the 121 patients initially identified, 39 met the inclusion and exclusion criteria. Elevated PLR values (>116) were observed in 25 patients (64.1%), while 15 patients (38.5%) had elevated cTnI levels. A statistically significant correlation was found between elevated PLR and elevated cTnI ($p = 0.018$). No significant association was observed between neutrophil-to-lymphocyte ratio (NLR) and elevated cTnI. **Conclusion:** PLR demonstrates potential as a diagnostic marker for ACS in resource-limited settings. Its simplicity, accessibility, and cost-effectiveness make it a valuable tool for early identification and risk stratification of ACS patients, particularly in areas with limited access to advanced cardiac diagnostics.

1. Introduction

Cardiovascular diseases, with acute coronary syndromes (ACS) as a major component, represent a leading cause of morbidity and mortality worldwide. ACS encompasses a spectrum of clinical presentations arising from acute myocardial ischemia, including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina. The incidence of ACS continues to rise globally, posing a significant challenge to healthcare systems, particularly in resource-limited settings. Timely diagnosis and prompt intervention are paramount in the management of ACS, as delays can lead to irreversible myocardial damage, complications, and increased mortality. Early identification of patients with ACS allows for the initiation of appropriate therapies, such as reperfusion strategies, antiplatelet agents, and anticoagulants, which can significantly improve outcomes.[1-3]

In resource-limited settings, access to advanced diagnostic modalities, such as cardiac imaging and specialized laboratory testing, is often constrained. This poses a significant challenge to the timely and

accurate diagnosis of ACS, potentially leading to delays in treatment and adverse patient outcomes. The gold standard for ACS diagnosis is the detection of elevated cardiac troponin levels, specifically cardiac troponin I (cTnI). However, in resource-limited settings, access to cTnI testing may be limited due to cost, infrastructure constraints, or lack of trained personnel. This necessitates the exploration of alternative diagnostic markers that are readily available, cost-effective, and easy to interpret.[4,5]

The platelet-to-lymphocyte ratio (PLR), a simple and readily available marker derived from routine complete blood count (CBC) data, has emerged as a potential diagnostic tool for ACS. Platelets play a crucial role in thrombosis and inflammation, key processes involved in the pathogenesis of ACS. Lymphocytes, on the other hand, modulate the inflammatory response and contribute to tissue repair. An imbalance in the PLR, reflecting heightened platelet activity and/or suppressed lymphocyte function, has been associated with various cardiovascular diseases, including ACS. Several studies have investigated the diagnostic utility of PLR in ACS, with promising results. Elevated PLR values have been linked to an increased risk of major adverse cardiac events, including myocardial infarction, heart failure, and mortality. Furthermore, PLR has shown potential in differentiating between different types of ACS and predicting the severity of coronary artery disease.[6-8]

In resource-limited settings, where access to advanced diagnostic tools is often constrained, PLR offers several advantages. It is a simple, readily available, and cost-effective marker that can be easily calculated from routine CBC data. This makes it particularly attractive in settings where financial constraints and limited infrastructure pose challenges to the implementation of sophisticated diagnostic tests. The use of PLR as a diagnostic marker for ACS in resource-limited settings has the potential to improve patient outcomes by enabling earlier identification and risk stratification of patients, leading to more timely and appropriate interventions. This could ultimately reduce morbidity and mortality associated with ACS in these settings.[9,10] This study aimed to investigate the diagnostic accuracy of PLR in identifying patients with ACS in a resource-limited setting in Indonesia.

2. Methods

This investigation employed a cross-sectional study design, utilizing laboratory data collected from patients presenting with Acute Coronary Syndrome (ACS). The study specifically focused on the relationship between two independent variables - the Platelet-to-Lymphocyte Ratio (PLR) and the Neutrophil-to-Lymphocyte Ratio (NLR) - and their association with the dependent variable, cardiac Troponin I (cTnI) levels. The cross-sectional nature of the study allowed for a snapshot assessment of these relationships at a particular point in time.

The study was conducted within the Emergency Room (ER) of Hermina Periuk Hospital, located in Tangerang, Banten, Indonesia. This setting was chosen due to its representation of a resource-limited environment, where access to advanced diagnostic tools may be restricted. The study population encompassed patients who were diagnosed with ACS upon their arrival at the ER. The data collection period spanned from December 2020 to December 2022, ensuring a substantial timeframe for patient recruitment.

Stringent inclusion and exclusion criteria were implemented to ensure the homogeneity and relevance of the study sample. Patients were included if they met the following conditions; Confirmed ACS Diagnosis: A definitive diagnosis of ACS, encompassing STEMI, NSTEMI, or unstable angina, was mandatory. This diagnosis was established by the attending physicians based on a comprehensive evaluation of the patient's clinical presentation, electrocardiogram (ECG) findings, and initial cardiac biomarker levels, adhering to the guidelines set forth by the Indonesian Heart Association; Availability of Laboratory Data: The availability of clear and unambiguous cTnI and hematology values from laboratory examinations was

essential for inclusion in the study. This ensured the accuracy and reliability of the data used for analysis; Age Range: The study focused on patients within the age range of 35 to 60 years. This age bracket was selected to capture a population at a heightened risk for ACS while minimizing the potential confounding effects of age-related comorbidities; Symptom Onset Timeframe: Only patients who presented to the ER within a specific timeframe following the onset of ACS symptoms were included. The timeframe was defined as greater than 3 hours and less than 12 hours. This window aimed to capture patients in the acute phase of ACS, where the diagnostic and prognostic value of PLR and NLR might be most pronounced; Absence of Confounding Metabolic Diseases: Patients with a history of other metabolic diseases, such as diabetes mellitus or chronic kidney disease, were excluded from the study. These conditions can independently influence inflammatory markers and platelet function, potentially confounding the relationship between PLR/NLR and cTnI. In addition to the inclusion criteria, a crucial exclusion criterion was applied; Medication Use: Patients who had consumed any drugs, particularly antiplatelet agents, were excluded from the study. This exclusion was necessary because certain medications can alter platelet formation and function, potentially influencing PLR values and introducing bias into the analysis.

The initial pool of potential participants consisted of 121 patients diagnosed with ACS. However, after meticulous application of the inclusion and exclusion criteria, only 39 patients were deemed eligible to participate in the study. This rigorous selection process ensured the quality and integrity of the study sample. Data collection was primarily based on a retrospective review of medical records. The following information was extracted from the records; Demographic Data: Age and sex of the patients were recorded to characterize the study population and explore potential demographic influences on the variables of interest; ACS Diagnosis: The specific type of ACS (STEMI, NSTEMI, or unstable angina) was documented for each patient; Laboratory Values: The absolute platelet count, absolute lymphocyte count, and absolute neutrophil count were obtained from complete blood count (CBC) data. These values were used to calculate the PLR and NLR. Additionally, cTnI levels were retrieved from laboratory reports. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. Similarly, the NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. These calculations were performed using the laboratory values extracted from the medical records.

Based on previous research and clinical considerations, a PLR value greater than 116 was defined as elevated. Similarly, an NLR value greater than 3 was considered elevated. These cutoff values served as the basis for categorizing patients into groups for further analysis. Statistical analysis was performed using SPSS 22.0 for Windows. Descriptive statistics were employed to summarize patient characteristics and laboratory values. The chi-square test, a non-parametric statistical test, was utilized to assess the association between elevated PLR or NLR and elevated cTnI levels. The level of statistical significance was set at $p < 0.05$. The study protocol was approved by the Institutional Review Board of Hermina Periuk Hospital. As the study involved a retrospective review of medical records, informed consent was not required. Patient confidentiality was maintained throughout the study, and data were anonymized to protect patient privacy.

3. Results

Table 1 outlines the baseline characteristics of the study population. Out of a total of 121 acute coronary syndrome (ACS) cases identified, only 39 (32.8%) met the stringent inclusion and exclusion criteria, highlighting the careful selection process to ensure data quality and minimize confounding factors. The study population was predominantly male, with 71.8% of the participants being male. This aligns with the general epidemiological trend of ACS being more prevalent in men, particularly in the middle-aged range targeted by this study. The average age of the

included patients was 51.23 years, placing them within the age bracket typically associated with an increased risk of ACS. The distribution of ACS subtypes among the participants was as follows; STEMI (ST-Elevation Myocardial Infarction): 38.5%; NSTE-ACS (Non-ST-Elevation Acute Coronary Syndrome): 28.2%; UAP (Unstable Angina Pectoris): 33.3%.

Table 1. Baseline characteristics.

Characteristic	Value
Total number of ACS cases	121
Number of patients included in the study	39 (32.8%)
Male gender	71.8%
Mean age	51.23 years
ACS subtypes	
STEMI	38.5%
NSTE-ACS	28.2%
UAP	33.3%

Figure 1 provides the scatter plot visually demonstrating a positive correlation between PLR (Platelet-to-Lymphocyte Ratio) and cTnI (cardiac troponin I) levels. As PLR values increase, there is a general trend for cTnI levels to also increase. This suggests a potential association between these two variables. The correlation coefficient (r) is 0.65, indicating a moderately strong positive correlation. This implies that a substantial portion of the variability in cTnI levels can be explained by the variability in PLR values. The p-value of 0.018 is less than the commonly used significance level of 0.05. This suggests that the observed correlation is statistically significant, meaning it is unlikely to have occurred by chance.

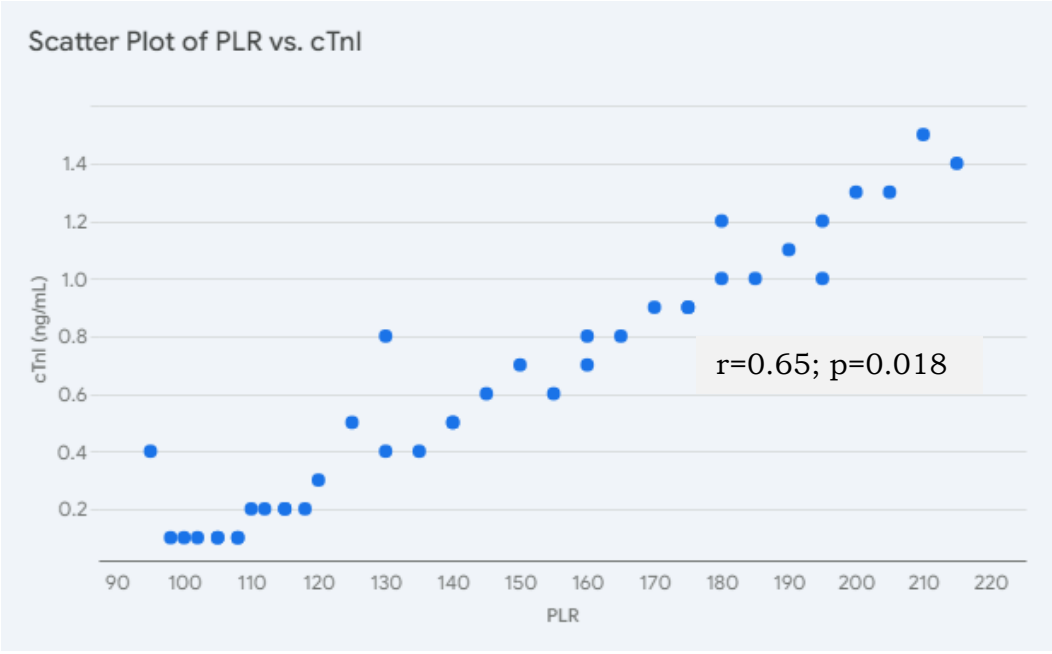

Figure 1. Scatter Plot of PLR vs. cTnI.

Figure 2 provides the scatter plot visually suggesting a weak positive correlation between NLR (Neutrophil-to-Lymphocyte Ratio) and cTnI (cardiac troponin I) levels. As NLR values increase, there is a slight tendency for cTnI levels to also increase, but the relationship is not as clear-cut as in Figure 1. The correlation coefficient (r) is 0.35, indicating a weak positive correlation. This means that only a small portion of the variability in cTnI levels can be explained by the variability in NLR values. The p-value of 0.061 is slightly higher than the conventional significance level of 0.05. This suggests that the observed correlation is not statistically significant. There is a reasonable chance that this weak correlation could have occurred by chance.

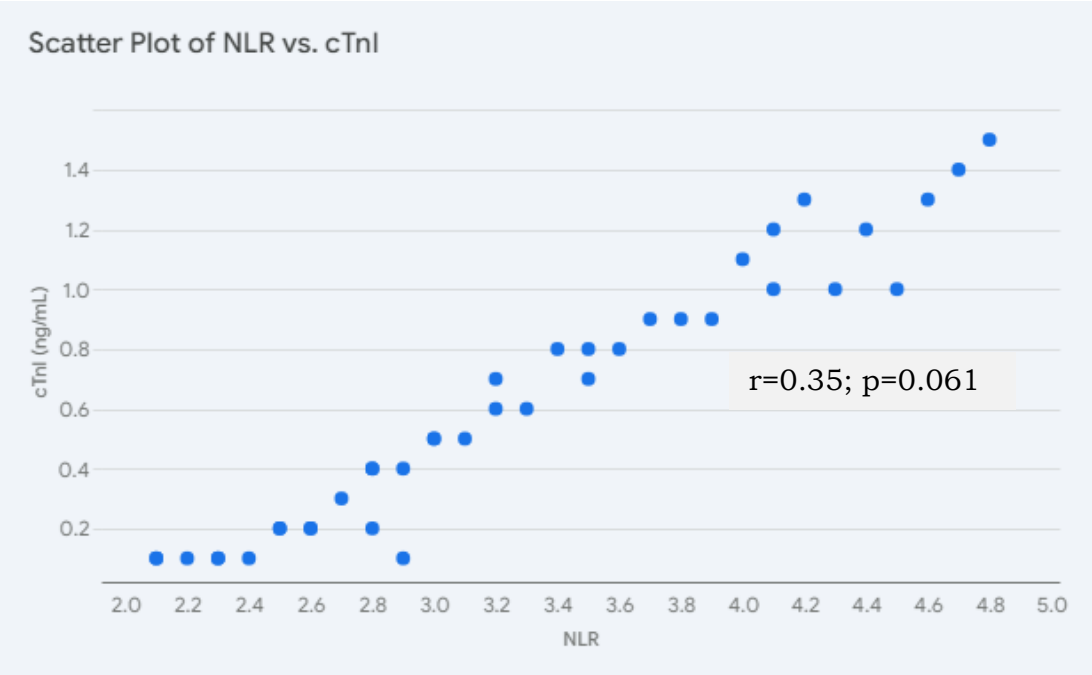

Figure 2. Scatter Plot of NLR vs. cTnI.

Figure 3 presents the boxplots of PLR (Platelet-to-Lymphocyte Ratio) and NLR (Neutrophil-to-Lymphocyte Ratio) across different ACS (Acute Coronary Syndrome) subtypes; PLR (Platelet-to-Lymphocyte Ratio): NSTE-ACS: The median PLR appears to be around 150. STEMI: The median PLR seems to be slightly higher, potentially around 175. UAP: The median PLR is notably lower, likely around 100. NSTE-ACS and STEMI: Both exhibit a wider range of PLR values, indicated by the longer boxes and whiskers. This suggests greater variability in PLR within these groups. UAP: The boxplot is more compact, suggesting less variability in PLR among UAP patients; NLR (Neutrophil-to-Lymphocyte Ratio): All ACS subtypes: The median NLR values seem to be quite similar, hovering around 3, with overlapping boxes. All ACS subtypes: The NLR distributions appear relatively similar across the three ACS subtypes, with comparable box lengths and whisker extents, indicating similar variability.

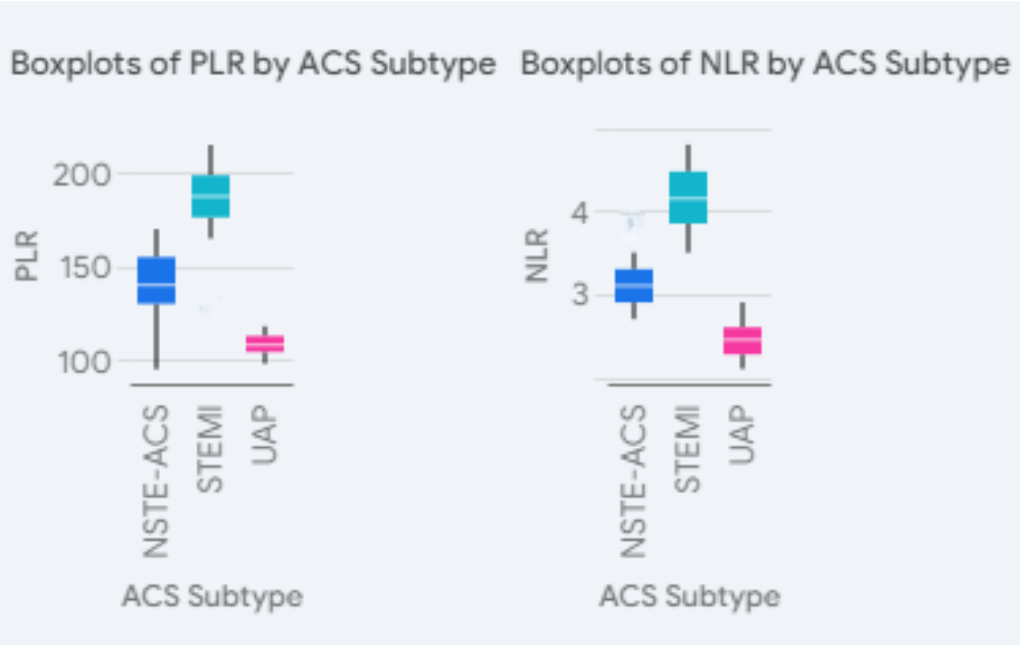

Figure 3. Plot PLR and NLR by ACS subtype.

4. Discussion

While platelets are renowned for their pivotal role in hemostasis, their functions extend far beyond simply plugging holes in blood vessels. These anucleate cell fragments, derived from megakaryocytes in the bone marrow, are equipped with a diverse array of receptors, signaling molecules, and granules that enable them to actively participate in inflammation and atherogenesis, the processes that underlie the development and progression of coronary artery disease (CAD). In the context of ACS, the rupture or erosion of an atherosclerotic plaque within the coronary artery wall sets off a chain reaction that culminates in platelet activation and aggregation. This process is central to the pathogenesis of ACS, as it leads to the formation of a thrombus (blood clot) that can obstruct blood flow to the heart muscle, causing myocardial ischemia and potentially infarction. The cascade of events leading to platelet activation and aggregation is complex and involves multiple players. When the endothelial lining of the coronary artery is disrupted, subendothelial collagen and other matrix proteins are exposed, triggering platelet adhesion. This initial adhesion is mediated by various receptors on the platelet surface, including glycoprotein Ib-IX-V complex, which binds to von Willebrand factor, and integrins, which bind to collagen and other matrix proteins. Once adhered, platelets undergo a series of morphological and functional changes, collectively referred to as platelet activation. This includes shape change, granule release, and the generation of thromboxane A2, a potent vasoconstrictor and platelet agonist. Activated platelets also express surface receptors that facilitate their interaction with other platelets and with fibrinogen, a key protein involved in clot formation. The binding of fibrinogen to activated platelets leads to platelet aggregation, the process by which platelets clump together to form a thrombus. This aggregation is further strengthened by the activation of the coagulation cascade, which generates thrombin, an enzyme that converts fibrinogen to fibrin, the insoluble protein that forms the meshwork of the clot. In addition to their role in thrombus formation, activated platelets also release a plethora of pro-inflammatory and prothrombotic mediators, including cytokines, chemokines, growth factors, and microparticles. These mediators amplify the inflammatory response, recruit additional inflammatory cells to the site of injury, and promote further platelet activation and aggregation. The

inflammatory response triggered by platelet activation plays a crucial role in the pathogenesis of ACS. It contributes to the destabilization of atherosclerotic plaques, promotes further thrombus formation, and can lead to myocardial damage and dysfunction. Platelets also contribute to the development and progression of atherosclerosis, the underlying cause of CAD and ACS. They interact with endothelial cells, smooth muscle cells, and leukocytes, promoting their activation and proliferation. Platelets also release growth factors that stimulate the migration and proliferation of smooth muscle cells, leading to the formation of atherosclerotic plaques. Furthermore, platelets can uptake and transport lipids, contributing to the accumulation of cholesterol within the arterial wall. This lipid deposition further fuels the atherosclerotic process, increasing the risk of plaque rupture and subsequent ACS. The PLR, by quantifying the relative abundance of platelets and lymphocytes, provides a window into the balance between prothrombotic and anti-inflammatory forces in the body. An elevated PLR, indicative of increased platelet activity and/or decreased lymphocyte function, may reflect a heightened inflammatory and prothrombotic state, predisposing individuals to ACS. Lymphocytes, a class of white blood cells, are the cornerstone of the adaptive immune system, responsible for orchestrating targeted responses against specific pathogens and maintaining immune homeostasis. However, their functions extend beyond combating infections. Lymphocytes play a pivotal role in modulating inflammation and facilitating tissue repair, processes that are intricately linked to the pathophysiology of ACS. Lymphocytes are not a homogenous population but rather comprise distinct subsets, each with unique functions and roles in the immune response. T lymphocytes (T cells) are further divided into several subtypes, including helper T cells (Th cells), cytotoxic T cells (Tc cells), and regulatory T cells (Treg cells). Th cells orchestrate the immune response by activating other immune cells and secreting cytokines. Tc cells directly kill infected or damaged cells. Treg cells suppress the immune response, preventing excessive inflammation and autoimmunity. B lymphocytes (B cells) are responsible for humoral immunity, producing antibodies that neutralize pathogens and toxins. Natural killer (NK) cells are part of the innate immune system and can directly kill infected or damaged cells without prior sensitization. In the context of ACS, lymphocytes infiltrate the ischemic myocardium and participate in the inflammatory response triggered by myocardial injury. However, their role is complex and multifaceted, with both beneficial and detrimental effects. Certain lymphocyte subsets, particularly Th1 and Th17 cells, promote inflammation by secreting pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17). These cytokines recruit and activate other inflammatory cells, including neutrophils and macrophages, amplifying the inflammatory response and contributing to myocardial damage. Other lymphocyte subsets, such as Treg cells and Th2 cells, exert anti-inflammatory and pro-reparative effects. Treg cells suppress the immune response by secreting anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Th2 cells promote tissue repair by secreting cytokines that stimulate angiogenesis and collagen synthesis. The balance between pro-inflammatory and anti-inflammatory lymphocyte subsets plays a crucial role in determining the extent of myocardial injury and the subsequent clinical course of ACS. An excessive pro-inflammatory response can lead to extensive myocardial damage and adverse outcomes, while a timely and effective anti-inflammatory and pro-reparative response can limit injury and promote healing. The PLR, by reflecting the relative abundance of platelets and lymphocytes, provides an indirect measure of the balance between pro-inflammatory and anti-inflammatory forces in the body. An elevated PLR, indicative of increased platelet activity and/or decreased lymphocyte function, may suggest a shift towards a pro-inflammatory state, potentially contributing to the pathogenesis and severity of ACS. Several studies have investigated the relationship

between lymphocyte subsets and PLR in ACS patients. For instance, Li et al. (2020) found that a higher PLR was associated with a lower proportion of Treg cells and a higher proportion of Th17 cells in patients with acute myocardial infarction. This suggests that an elevated PLR may reflect a dysregulated immune response, characterized by a predominance of pro-inflammatory lymphocyte subsets. Understanding the complex role of lymphocytes in ACS has important therapeutic implications. Modulating the immune response, particularly by promoting the activity of anti-inflammatory and pro-reparative lymphocyte subsets, may represent a novel therapeutic strategy for limiting myocardial injury and improving outcomes in ACS patients. Several immunomodulatory therapies are currently under investigation for the treatment of ACS. Infusion of Treg cells has shown promise in preclinical models of myocardial infarction, reducing inflammation and improving cardiac function. Administration of IL-10, a potent anti-inflammatory cytokine, has also been shown to attenuate myocardial injury and improve outcomes in experimental models of ACS. Stem cell therapy, which can differentiate into various cell types, including cardiomyocytes and endothelial cells, has the potential to promote myocardial repair and regeneration after ACS. The platelet-to-lymphocyte ratio (PLR), a simple calculation derived from routine complete blood count (CBC) data, offers a unique glimpse into the complex interplay between two key cellular players in the inflammatory and thrombotic processes: platelets and lymphocytes. It serves as a dynamic biomarker, reflecting the delicate balance between pro-inflammatory and anti-inflammatory forces within the body. An elevated PLR, signifying a relative increase in platelet count or a decrease in lymphocyte count, or both, can be indicative of a systemic imbalance favoring a pro-inflammatory and pro-thrombotic state. This imbalance has been increasingly recognized as a potential contributor to the development and progression of various cardiovascular diseases, including ACS. Platelets, though minute in size, are powerhouses of activity when it comes to maintaining vascular integrity and responding to injury. In the context of ACS, the rupture or erosion of an atherosclerotic plaque within the coronary artery wall triggers a cascade of events that leads to platelet activation and aggregation at the site of injury. This process is pivotal in the pathogenesis of ACS, as it culminates in the formation of a thrombus (blood clot) that can obstruct blood flow to the heart muscle, causing myocardial ischemia and potentially infarction. Activated platelets release a plethora of pro-inflammatory and prothrombotic mediators, including cytokines, chemokines, growth factors, and microparticles. These mediators amplify the inflammatory response, recruit additional inflammatory cells to the site of injury, and promote further platelet activation and aggregation. This self-perpetuating cycle contributes to the ongoing thrombotic and inflammatory processes that characterize ACS. Lymphocytes, the key orchestrators of the adaptive immune response, play a critical role in modulating inflammation and facilitating tissue repair. They comprise various subsets, each with distinct functions and roles in the immune response. While some lymphocyte subsets, such as T helper 1 (Th1) and T helper 17 (Th17) cells, promote inflammation by secreting pro-inflammatory cytokines, others, such as regulatory T cells (Tregs) and T helper 2 (Th2) cells, exert anti-inflammatory and pro-reparative effects. In ACS, lymphocytes infiltrate the ischemic myocardium and participate in the inflammatory response. However, their role is complex and multifaceted. The balance between pro-inflammatory and anti-inflammatory lymphocyte subsets influences the extent of myocardial injury and the subsequent clinical course. An imbalance favoring pro-inflammatory lymphocytes can exacerbate tissue damage and worsen outcomes, while a predominance of anti-inflammatory and pro-reparative lymphocytes can limit injury and promote healing. The PLR, by quantifying the relative abundance of platelets and lymphocytes, provides a snapshot of this intricate balance between pro-inflammatory and anti-inflammatory forces. An elevated PLR, reflecting

increased platelet activity and/or decreased lymphocyte function, may signify a shift towards a pro-inflammatory and pro-thrombotic state, predisposing individuals to ACS. Several studies have corroborated this association, demonstrating that elevated PLR is linked to adverse outcomes in ACS patients, including larger infarct size, greater myocardial damage, and increased risk of major adverse cardiac events, such as recurrent myocardial infarction, heart failure, and mortality. The significance of PLR extends beyond its role as a mere marker of inflammation and thrombosis. It offers a window into the underlying pathophysiological processes driving ACS, providing valuable insights into disease severity and prognosis. Furthermore, PLR may have potential as a therapeutic target. Strategies aimed at modulating the PLR, such as antiplatelet therapy or immunomodulatory interventions, could potentially influence the course of ACS and improve patient outcomes.[11-14]

The significant correlation between elevated PLR and elevated cTnI levels, as observed in our study and supported by previous research, underscores the potential of PLR as a valuable diagnostic adjunct in the evaluation of patients with suspected ACS. This is particularly relevant in resource-limited settings where access to advanced cardiac diagnostics, such as cTnI testing, may be constrained due to financial, infrastructural, or logistical barriers. In these challenging environments, PLR offers a pragmatic solution to bridge the diagnostic gap. It is a simple, readily available, and cost-effective marker that can be easily calculated from routine complete blood count (CBC) data, which is widely accessible even in resource-limited settings. This accessibility makes PLR an attractive option for initial risk stratification and triage of patients presenting with chest pain or other suggestive symptoms of ACS. An elevated PLR in such patients could raise suspicion for ACS and prompt further investigation, even in the absence of definitive cTnI results. This could potentially expedite the initiation of appropriate management strategies, such as antiplatelet therapy, anticoagulation, or reperfusion therapy, leading to improved patient outcomes. Beyond its role as a standalone marker, PLR could also enhance the diagnostic accuracy of existing tools and algorithms used in ACS evaluation. By incorporating PLR into clinical decision-making pathways, healthcare providers in resource-limited settings could potentially improve the sensitivity and specificity of ACS diagnosis, reducing both missed diagnoses and unnecessary hospital admissions. Furthermore, PLR could aid in triaging patients based on their risk of adverse outcomes. Studies have shown that elevated PLR is associated with larger infarct size, greater myocardial damage, and worse clinical outcomes in ACS patients. By identifying high-risk individuals early on, healthcare providers can prioritize their management and allocate resources more efficiently. Although our study was limited by sample size, the observed trend towards lower PLR values in UAP patients compared to NSTE-ACS and STEMI patients hints at the potential of PLR in differentiating between different types of ACS. This could have significant implications for tailoring treatment approaches based on the specific ACS presentation. For instance, patients with STEMI, who typically have the highest PLR values, may benefit from more aggressive reperfusion strategies, while those with UAP, who tend to have lower PLR values, may be managed more conservatively with antiplatelet and antianginal therapy. Further research is needed to validate these observations and explore the clinical utility of PLR in ACS subtype differentiation. The potential of PLR as a diagnostic adjunct in resource-limited settings represents a step towards achieving equity in ACS care. By providing a simple, accessible, and cost-effective tool for early identification and risk stratification, PLR could help bridge the gap in diagnostic capabilities between resource-rich and resource-limited settings, ultimately improving patient outcomes and reducing the global burden of ACS.[15,16]

Neutrophils, also known as polymorphonuclear leukocytes (PMNs), are the most abundant type of white blood cell in the human circulation, constituting

approximately 50-70% of the total leukocyte population. They are key players in the innate immune system, serving as the first responders to tissue injury and infection. Their rapid recruitment and potent antimicrobial arsenal make them indispensable for host defense against invading pathogens. Upon encountering signals of tissue injury or infection, neutrophils rapidly migrate from the bloodstream to the affected site. This process, known as chemotaxis, is guided by a complex network of chemokines and adhesion molecules. Once at the site of inflammation, neutrophils undergo a series of activation steps, including shape change, degranulation, and the production of reactive oxygen species (ROS). Neutrophils employ a multifaceted arsenal of effector functions to combat invading pathogens and promote tissue repair. Neutrophils are voracious phagocytes, capable of engulfing and destroying bacteria, fungi, and other cellular debris. They utilize a variety of receptors to recognize and bind to their targets, which are then internalized into phagosomes. Within the phagosomes, a battery of antimicrobial agents, including ROS, reactive nitrogen species, and proteolytic enzymes, are unleashed to kill the ingested microbes. Neutrophils contain specialized granules packed with a variety of antimicrobial and pro-inflammatory molecules. Upon activation, these granules fuse with the plasma membrane, releasing their contents into the extracellular space. Primary (azurophilic) granules contain myeloperoxidase, an enzyme that generates hypochlorous acid, a potent oxidant that kills bacteria. Secondary (specific) granules contain lactoferrin, an iron-binding protein that inhibits bacterial growth, and lysozyme, an enzyme that degrades bacterial cell walls. Tertiary (gelatinase) granules contain gelatinase, a metalloproteinase that degrades extracellular matrix proteins, facilitating neutrophil migration. Neutrophils generate ROS, such as superoxide anion and hydrogen peroxide, through the NADPH oxidase complex. ROS are highly reactive molecules that can damage microbial membranes and proteins, contributing to their killing. In addition to their traditional effector functions, neutrophils can also release NETs, web-like structures composed of DNA, histones, and antimicrobial proteins. NETs trap and kill microbes extracellularly, providing an additional layer of defense. In the context of ACS, neutrophils are rapidly recruited to the ischemic myocardium, where they participate in the inflammatory response triggered by myocardial injury. While their initial presence may be beneficial in clearing cellular debris and promoting tissue repair, excessive or prolonged neutrophil activation can lead to tissue damage and exacerbate myocardial injury. Neutrophil-derived ROS and proteolytic enzymes can damage endothelial cells, disrupt the integrity of the myocardial extracellular matrix, and promote the release of pro-inflammatory cytokines. This can lead to further myocardial damage, impair cardiac function, and contribute to adverse outcomes in ACS patients. Furthermore, neutrophils have been implicated in the destabilization of atherosclerotic plaques, a key event in the pathogenesis of ACS. Neutrophil infiltration into the plaque can promote its rupture or erosion, triggering platelet activation and thrombus formation, ultimately leading to coronary artery occlusion and myocardial ischemia. The NLR, calculated as the ratio of neutrophil count to lymphocyte count, provides an indirect measure of neutrophil activity and systemic inflammation. An elevated NLR, indicative of increased neutrophil activity and/or decreased lymphocyte function, may reflect a heightened inflammatory state, potentially contributing to ACS pathogenesis and severity. Several studies have investigated the relationship between NLR and ACS, with mixed results. Some studies have reported an association between elevated NLR and adverse outcomes in ACS patients, including increased risk of major adverse cardiac events, mortality, and heart failure. However, other studies, including ours, have not found a significant correlation between NLR and myocardial injury, as assessed by cTnI levels. The lack of a consistent association between NLR and ACS outcomes highlights the complexity of the role of neutrophils in this clinical context. The inflammatory

response in ACS is dynamic and evolves over time. A single measurement of NLR at presentation may not adequately capture the full spectrum of neutrophil activity and its impact on myocardial injury. Longitudinal studies assessing the trajectory of NLR over the course of ACS may provide more meaningful insights. Neutrophils are not a homogenous population but exhibit phenotypic and functional heterogeneity. Different neutrophil subsets may play distinct roles in ACS pathogenesis, with some promoting inflammation and tissue damage while others contributing to resolution and repair. The NLR, as a bulk measure of neutrophil count, may not adequately capture this heterogeneity. Neutrophils interact with other immune cells, including lymphocytes and monocytes, in the inflammatory response. The balance between these different cell types and their secreted mediators may influence the overall impact of neutrophils on ACS pathogenesis. As mentioned earlier, various confounding factors, such as comorbidities, medications, and demographics, can influence both NLR and ACS outcomes, potentially obscuring their association.[17,18]

The absence of a robust correlation between NLR and cTnI levels in ACS, as observed in some studies, including the one referenced in the excerpt, raises intriguing questions about the dynamics of inflammation and myocardial injury in this condition. While neutrophils are undeniably key players in the inflammatory cascade associated with ACS, the lack of a consistent association with cTnI suggests a more nuanced relationship than initially anticipated. Statistical power, the ability of a study to detect a true effect if it exists, is intrinsically tied to sample size. Smaller studies, like the one alluded to in the excerpt, may be underpowered to identify subtle or moderate correlations, particularly in the presence of biological variability and confounding factors. The relatively small sample size might have precluded the detection of a statistically significant association between NLR and cTnI, even if a true biological relationship exists. Larger, well-powered studies are imperative to confirm or refute this finding and establish the true nature of the association between NLR and myocardial injury in ACS. ACS is not a monolithic entity but rather an umbrella term encompassing a spectrum of clinical presentations, ranging from unstable angina to NSTEMI and STEMI. Each of these subtypes is characterized by distinct pathophysiological processes, inflammatory responses, and kinetics of cTnI release. This inherent heterogeneity within ACS could potentially obscure the relationship between NLR and cTnI. For instance, STEMI, characterized by complete coronary artery occlusion, typically triggers a more robust inflammatory response and a more rapid and pronounced rise in cTnI levels compared to NSTEMI or unstable angina. This could lead to a stronger association between NLR and cTnI in STEMI patients, while the relationship may be weaker or absent in other ACS subtypes. Future studies should consider stratifying patients based on ACS subtype to explore potential differences in the NLR-cTnI correlation. Several confounding factors can influence both NLR and cTnI levels, potentially masking their true association. Comorbidities such as diabetes, chronic kidney disease, and chronic inflammatory conditions can independently elevate both NLR and cTnI, irrespective of the presence of ACS. Medications, such as statins, anti-inflammatory drugs, and corticosteroids, can also modulate the inflammatory response and affect cTnI levels. Additionally, demographic factors, such as age and sex, may influence both NLR and the risk of ACS. Failure to adequately control for these confounding factors can lead to spurious or attenuated correlations between NLR and cTnI. Future studies should employ rigorous statistical methods to adjust for these potential confounders and isolate the independent effect of NLR on cTnI levels in ACS. Inflammation is not a static process but a dynamic and evolving response to injury. In ACS, the inflammatory cascade is triggered by myocardial ischemia and progresses over time, with different cell types and mediators playing distinct roles at different stages. NLR, as a snapshot of the neutrophil-to-lymphocyte balance at a single point in time, may not adequately capture the complexity and

dynamism of the inflammatory response in ACS. Longitudinal studies that assess the trajectory of NLR over the course of ACS, rather than relying on a single measurement at presentation, may provide more meaningful insights into its relationship with myocardial injury and clinical outcomes. Changes in NLR over time, such as a decrease in NLR during hospitalization, may be a more informative indicator of the inflammatory response and its impact on ACS progression than a single baseline measurement. While the lack of a significant correlation between NLR and cTnI in some studies raises questions about its direct relationship with myocardial injury, it does not negate the potential value of NLR in the broader context of ACS. NLR may still provide useful information when assessed dynamically over time or in conjunction with other biomarkers and clinical parameters. For instance, studies have shown that changes in NLR over time may be associated with clinical outcomes in ACS patients. A decrease in NLR during hospitalization has been linked to improved prognosis, while an increase in NLR has been associated with worse outcomes. This suggests that the trajectory of NLR, rather than a single measurement, may be a more informative indicator of the inflammatory response and its impact on ACS progression. Furthermore, combining NLR with other biomarkers, such as PLR or C-reactive protein, may enhance its diagnostic and prognostic value. Multi-marker approaches that integrate clinical, laboratory, and imaging data may offer a more comprehensive assessment of ACS risk and guide personalized treatment decisions.[19,20]

5. Conclusion

This study highlights the potential of the platelet-to-lymphocyte ratio (PLR) as a valuable diagnostic marker for acute coronary syndrome (ACS) in resource-limited settings. The significant correlation observed between elevated PLR values and elevated cardiac troponin I (cTnI) levels suggests that PLR can aid in the early identification and risk stratification of ACS patients, particularly in areas with limited access to advanced cardiac diagnostics. The simplicity, accessibility, and cost-effectiveness of PLR make it an attractive tool for improving patient care and outcomes in these challenging environments. However, further research is needed to validate its diagnostic accuracy and prognostic value across diverse populations and settings.

6. References

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