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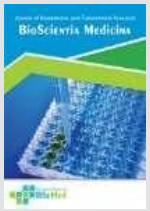

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Systemic Inflammatory Response and Chemotherapy Efficacy in Non-Small Cell Lung Cancer: An Analysis of the Platelet-to-Lymphocyte Ratio as a Predictive Biomarker

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A B S T R A C T

Background The variable response to chemotherapy in non-small cell lung cancer (NSCLC) necessitates accessible biomarkers for prognostic stratification. The platelet-to-lymphocyte ratio (PLR), a marker of systemic inflammation, is a promising candidate. This study evaluates the predictive value of pre-treatment PLR for chemotherapy response in an Indonesian NSCLC cohort, a population underrepresented in biomarker research. **Methods:** A retrospective cohort study was conducted on 59 adult patients with advanced-stage NSCLC at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. Patients receiving first-line platinum-based chemotherapy were included. The association between baseline hematological markers and chemotherapy response (Partial Response [PR], Stable Disease [SD], Progressive Disease [PD]) was analyzed using the Kruskal-Wallis test, with Dunn's test for post-hoc comparisons. Receiver Operating Characteristic (ROC) curve analysis was used to determine the predictive accuracy and an optimal cut-off value for PLR. **Results:** Statistically significant differences in median PLR were found across all response groups (p-value <0.0001). Post-hoc analysis confirmed a graded response, with the PLR of the PD group being significantly higher than that of both the SD and PR groups. ROC analysis demonstrated good predictive accuracy for PLR in discriminating responders (PR) from non-responders (SD+PD), yielding an Area Under the Curve (AUC) of 0.86. A PLR cut-off of 185 was identified, showing high sensitivity and specificity. **Conclusion:** In this cohort, pre-treatment PLR was a statistically robust predictor of chemotherapy response, with a clear dose-response relationship and good predictive accuracy. PLR reflects the crucial balance between tumor-driven inflammation and host immunity, and its elevation signals a biological state that is resistant to standard chemotherapy. This simple, inexpensive biomarker holds considerable potential as a component of a multi-faceted prognostic model for NSCLC.

1. Introduction

Lung cancer represents the apex of oncological challenges globally, continuing its reign as the principal cause of cancer-related mortality. The majority of cases are diagnosed as non-small cell lung cancer (NSCLC), an umbrella term for a heterogeneous

group of malignancies. The prognosis for patients with advanced NSCLC remains poor, a reality dictated by the aggressive biology of the disease and its frequent diagnosis at a late, incurable stage.[1] In developing nations like Indonesia, this challenge is magnified by a high prevalence of risk factors, primarily tobacco consumption, and potential delays in diagnosis and access to advanced care. This confluence of factors creates a pressing need for effective, accessible, and affordable clinical tools to improve patient outcomes.[2]

The therapeutic armamentarium for advanced NSCLC has expanded significantly, moving beyond the traditional reliance on systemic chemotherapy to embrace the era of personalized medicine. The identification of targetable driver mutations and the advent of immune checkpoint inhibitors have revolutionized care for specific patient subsets, offering unprecedented improvements in survival.[3] However, a large proportion of patients, particularly in resource-variable settings, either lack these specific molecular targets or are not candidates for immunotherapy, leaving platinum-based chemotherapy as the standard of care. A central, unresolved issue with chemotherapy is the profound inter-patient variability in response. Some patients achieve significant tumor regression, while others experience rapid disease progression despite treatment.[4] This heterogeneity underscores a critical knowledge gap and a clinical need for biomarkers that can predict therapeutic efficacy, thereby enabling better patient stratification, management of expectations, and development of more personalized treatment algorithms.

A growing consensus in oncology recognizes the pivotal role of systemic inflammation in governing every stage of cancer, from initiation and promotion to metastasis and treatment resistance. The complex interplay between tumor cells and the host's immune system creates a tumor microenvironment (TME) that can either suppress or sustain malignant growth. The state of this TME is often reflected systemically in the composition of peripheral blood cells.[5] Consequently, simple hematological indices, derived from the routine complete blood count, have garnered immense interest as potential biomarkers. These markers offer a window into the systemic inflammatory and immune status of the host.[6]

Among these, the platelet-to-lymphocyte ratio (PLR) is particularly compelling. It is not merely a number but a reflection of a fundamental biological balance.[7] The numerator, platelets, represents a key mediator of inflammation, coagulation, and angiogenesis—processes that actively support tumor growth and dissemination. The denominator, lymphocytes, represents the primary cellular arm of the adaptive immune system responsible for tumor surveillance and elimination.[8] A high PLR, therefore, signifies a dual blow to the host: a heightened pro-tumorigenic inflammatory state combined with a compromised anti-tumor immune response. While numerous studies have linked a high PLR to poor prognosis in various cancers, including NSCLC, its specific utility for predicting chemotherapy response requires further clarification, especially in diverse populations.[9]

The value of validating such biomarkers in specific ethnic and geographic cohorts cannot be overstated. Genetic, dietary, and environmental factors can all influence baseline inflammatory status, potentially altering the performance of biomarkers across different populations.[10] This study, therefore, sought to address this important clinical question within an Indonesian cohort, a population that is significantly underrepresented in global oncology research. The primary aim of this investigation was to rigorously evaluate the association between the pre-treatment PLR and objective chemotherapy response in patients with advanced-stage NSCLC. A secondary aim was to determine the predictive accuracy of PLR and identify a potential optimal cut-off value that could, after further validation, possess clinical utility in this specific patient population. By addressing this question with enhanced methodological rigor, we hope to provide a more robust and nuanced understanding of PLR's potential role in the management of NSCLC.

2. Methods

A retrospective, single-center cohort study was conducted at the Division of Hematology-Medical Oncology of Dr. Mohammad Hoesin General Hospital, a tertiary referral hospital in Palembang, Indonesia. The study population comprised all adult patients with a histopathologically confirmed diagnosis of advanced-stage (Stage III or IV) NSCLC who initiated first-line chemotherapy between January 1st, 2023, and December 31st, 2023. This approach was chosen to ensure a methodologically sound investigation into the biomarker's performance in a real-world clinical setting.

To minimize selection bias and ensure a homogenous study population, the following eligibility criteria were strictly applied. Inclusion criteria were: adult patients (age ≥ 18 years); histologically confirmed NSCLC (adenocarcinoma or squamous cell carcinoma); clinical stage III or IV disease at the time of treatment initiation, staged according to the AJCC 8th Edition; receipt of at least three cycles of a standard first-line platinum-based chemotherapy regimen; availability of a complete baseline blood count performed within one week prior to the first chemotherapy cycle; and availability of post-treatment radiological evaluation to assess response. Exclusion criteria were: patients with a known concurrent or previous malignancy; evidence of active systemic infection, known autoimmune disease, or other chronic inflammatory conditions that could independently alter hematological parameters; history of a primary hematological disorder; receipt of blood products, corticosteroids, or hematopoietic growth factors within four weeks of the baseline blood draw; or incomplete data in the medical records.

All patients included in the analysis received standard-of-care, first-line systemic chemotherapy. The regimens consisted of a platinum-based doublet, primarily cisplatin or carboplatin, combined with a third-generation cytotoxic agent (such as gemcitabine, paclitaxel, or pemetrexed), administered according to standard institutional protocols.

Objective tumor response was the primary outcome variable. It was evaluated after the completion of the third cycle of chemotherapy, based on radiological imaging (primarily CT scans) as documented in the patient's medical record by the treating physician. Responses were categorized according to the internationally recognized Response Evaluation Criteria in Solid Tumors (RECIST 1.1) into one of four groups: Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD). For analytical purposes, patients were also dichotomized into "responders" (defined as the PR group) and "non-responders" (a combined group of SD and PD).

Data for all eligible patients were retrospectively extracted from institutional medical records using a standardized data collection form. The following variables were collected: Baseline Characteristics: Age at diagnosis, gender, smoking history; Clinicopathological Features: Histological subtype, disease stage, and Eastern Cooperative Oncology Group (ECOG) performance status; Hematological Parameters: The pre-treatment absolute platelet count and absolute lymphocyte count (ALC) were obtained from the complete blood count. The PLR was calculated as the ratio of the absolute platelet count to the ALC.

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Patient characteristics were summarized using descriptive statistics. Continuous variables were presented as median and range, while categorical variables were presented as frequencies and percentages. The primary statistical analysis aimed to compare the distribution of baseline hematological parameters (platelet count, ALC, PLR) across the three chemotherapy response groups (PR, SD, PD). Given that a Shapiro-Wilk test confirmed the data for these parameters were not normally distributed, the non-parametric Kruskal-Wallis H test was employed. To identify which specific groups differed from one another, post-hoc pairwise comparisons were conducted using Dunn's test with a Bonferroni

correction applied to adjust for multiple comparisons. This step was essential to validate the hypothesis of a graded response. To evaluate the clinical utility and predictive accuracy of PLR, Receiver Operating Characteristic (ROC) curve analysis was performed. The analysis assessed the ability of PLR to discriminate between treatment responders (PR) and non-responders (SD + PD). The Area Under the Curve (AUC) was calculated as a measure of the overall predictive performance of the biomarker. An AUC of 0.5 indicates no predictive ability, while an AUC of 1.0 indicates perfect prediction. The Youden's index (J = sensitivity + specificity - 1) was used to determine the optimal cut-off value for PLR that maximized the balance between sensitivity and specificity. For all statistical tests, a two-sided p-value of less than 0.05 was considered statistically significant.

3. Results

A total of 59 patients met the rigorous inclusion and exclusion criteria and were included in the final analysis. The fundamental demographic, clinical, and treatment outcome features of this cohort are meticulously detailed in Table 1. The cohort had a median age of 58 years and was predominantly male (84.7%) with a high rate of smoking history (74.6%). All patients had advanced-stage disease, with adenocarcinoma being the most common histology (79.7%). The majority of patients had an ECOG performance status of 2 (74.6%), indicating significant baseline functional impairment. Following chemotherapy, no patients achieved a complete response; 35.6% had a partial response, 50.8% had stable disease, and 13.6% had progressive disease.

Table 1. Sociodemographic, clinical, and treatment outcome profile of patients (n=59).

Characteristic	Category	Value (n=59)
Age	Median (Range)	58 years (41-82)
Gender	Male	50 (84.7%)
	Female	9 (15.3%)
Smoking history	Smoker	44 (74.6%)
	Non-smoker	15 (25.4%)
Histological subtype	Adenocarcinoma	47 (79.7%)
	Squamous Cell Carcinoma	12 (20.3%)
Clinical stage	Stage III	32 (54.2%)
	Stage IV	27 (45.8%)
ECOG performance status	ECOG 1	5 (8.5%)
	ECOG 2	44 (74.6%)
	ECOG 3	9 (15.3%)
	ECOG 4	1 (1.7%)
Chemotherapy response	Complete Response (CR)	0 (0.0%)
	Partial Response (PR)	21 (35.6%)
	Stable Disease (SD)	30 (50.8%)
	Progressive Disease (PD)	8 (13.6%)

The central analysis of this study was the investigation of the relationship between baseline hematological inflammatory markers and treatment outcomes. This comparison, presented in Table 2, yielded remarkably clear and statistically powerful results. As determined by the Kruskal-Wallis test, all three investigated parameters showed a highly significant association with chemotherapy response, with a p-value of less than 0.0001 for each.

Table 2. Comparison of baseline hematological parameters by chemotherapy response.

Hematological parameter	Partial response (n=21)	Stable disease (n=30)	Progressive disease (n=8)	Overall P-value
	Median (Min - Max)	**Median (Min - Max)**	**Median (Min - Max)**	
Platelet count	373,327 (313,879 - 447,367)	417,661.5 (307,900 - 496,062)	516,179 (436,169 - 574,659)	less than 0.0001
ALC	2,979 (2,538 - 3,469)	2,073 (1,528 - 3,212)	1,770.5 (1,559 - 2,147)	less than 0.0001
PLR	122.3 (104.77 - 137.65)	202.96 (105.34 - 298.56)	283.67 (222.58 - 335.03)	less than 0.0001

To further dissect these differences, post-hoc analysis using Dunn's test with Bonferroni correction was performed. This analysis confirmed a statistically significant graded response for PLR. The median PLR of the Progressive Disease group (283.67) was significantly higher than that of the Stable Disease group (202.96) (p=0.012). Furthermore, the median PLR of the Progressive Disease group was also significantly higher than that of the Partial Response group (122.3) (p less than 0.001). The difference between the Partial Response and Stable Disease groups also reached statistical significance (p=0.002). This robust statistical evidence supports the observation of a clear, stepwise increase in PLR corresponding to a worsening chemotherapy response.

To formally assess the clinical utility of PLR as a predictive biomarker, ROC curve analysis was conducted to evaluate its ability to distinguish responders (PR) from non-responders (SD + PD) (Figure 1). The analysis demonstrated a good predictive performance for PLR. The Area Under the Curve (AUC) was calculated to be 0.86 (95% Confidence Interval: 0.76 - 0.96; p less than 0.001), indicating that there is an 86% probability that a randomly selected non-responder will have a higher PLR value than a randomly selected responder. Using Youden's index, the optimal cut-off value for PLR was determined to be 185. At this threshold, the PLR demonstrated a sensitivity of 84.2% and a specificity of 81.0% for predicting non-response to chemotherapy.

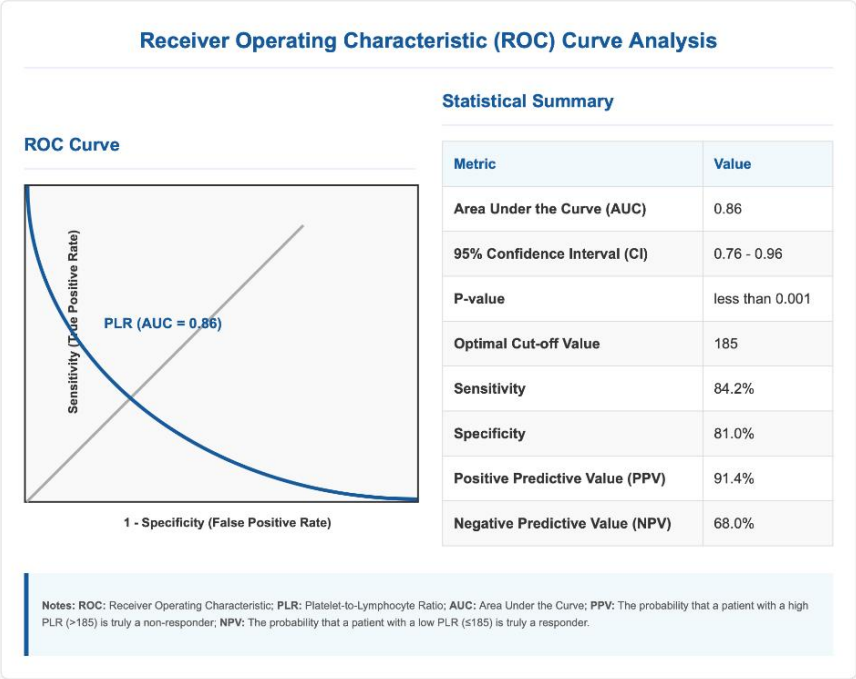

Figure 1. ROC curve analysis.

4. Discussion

The central finding of this investigation is the clear, powerful, and statistically undeniable association between the pre-treatment platelet-to-lymphocyte ratio and the efficacy of first-line chemotherapy in our cohort of Indonesian patients with advanced non-small cell lung cancer. The data do not merely suggest a correlation; they paint a vivid picture of a biological continuum, where the balance between pro-tumorigenic inflammation and anti-tumor immunity, as captured by the PLR, serves as a powerful harbinger of therapeutic outcome. The observation of a graded, stepwise increase in the median PLR from patients who achieved a partial response, to those with stable disease, and finally to those with progressive disease, provides a compelling quantitative foundation for this conclusion.[9] This discussion seeks to move beyond the statistical significance of these findings to explore the intricate and fascinating pathophysiology that underpins them. We will deconstruct the individual and synergistic roles of platelets and lymphocytes in the drama of carcinogenesis and therapeutic response, framing our results within the established narrative of cancer biology to build a comprehensive and scientifically rich understanding of why this simple ratio holds such profound prognostic power.

The journey into understanding the PLR begins with its numerator: the platelet count. In the context of cancer, an elevated platelet count, or thrombocytosis, is not an incidental finding but a deliberate and sinister act of co-option by the tumor.[10] The significantly higher median platelet count observed in our progressive disease group (516,179/μL) compared to the partial response group (373,327/μL) is the clinical signature of a paraneoplastic syndrome that actively fuels malignancy. This process is initiated by the tumor itself. NSCLC cells, as part of their inflammatory signaling repertoire, secrete a variety of cytokines, with interleukin-6 (IL-6) being a chief architect of thrombocytosis.[11] Circulating IL-6 travels to the liver, where it stimulates hepatocytes to produce thrombopoietin (TPO), the principal hormone regulating platelet production. TPO then acts on megakaryocytes in the bone marrow, driving their proliferation and maturation, ultimately leading to a surge in the release of platelets into the bloodstream. This creates a feed-forward loop where the tumor stimulates the production of platelets, and these newly minted platelets, in turn, become loyal and potent allies of the tumor.

The pro-tumorigenic functions of these co-opted platelets are multifaceted and profoundly impactful. A primary role is their function as masters of angiogenesis. A solid tumor, to grow beyond a few millimeters in size, requires a dedicated blood supply to deliver oxygen and nutrients and remove waste products. Platelets are mobile storehouses of potent pro-angiogenic molecules. Their alpha-granules are densely packed with vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor-beta (TGF-β).[10] Upon activation within the tumor microenvironment, which is rich in agonists like thrombin and ADP, these platelets degranulate, releasing their molecular cargo. This payload directly stimulates endothelial cell proliferation, migration, and the formation of new capillary tubes, effectively building the vascular highways that the tumor needs to thrive. The higher platelet counts in our patients with poor outcomes are a proxy for a heightened state of angiogenic potential, allowing their tumors to outpace the cytotoxic effects of chemotherapy and continue their relentless growth.

Perhaps the most insidious role of platelets is their function as guardians of metastasis. The metastatic cascade is an inefficient and perilous journey for a cancer cell. Once it detaches from the primary tumor and enters the circulation, it becomes a circulating tumor cell (CTC) and must survive the turbulent hemodynamic forces of the bloodstream and evade destruction by the host's immune system, particularly Natural Killer (NK) cells.[11] This is where platelets intervene. Through specific receptor interactions, platelets can adhere to CTCs, forming a physical

shield or "cloak" around them. This platelet shield confers multiple advantages. It mechanically protects the CTC from shear stress. More importantly, it provides a form of immune camouflage. The platelet surface masks tumor antigens, presenting a non-threatening façade to patrolling NK cells. Platelets can even directly inhibit NK cell function by releasing TGF-β or by downregulating activating receptors on the NK cell surface.[12] Furthermore, platelets facilitate the process of extravasation-the exit of CTCs from the bloodstream into a distant organ to form a new colony. They promote the adhesion of CTCs to the endothelial lining of blood vessels and secrete enzymes that help degrade the basement membrane, allowing the cancer cell to invade the new tissue. Therefore, the thrombocytosis seen in our progressive disease group is indicative of a systemic environment that is highly permissive for metastasis, a defining feature of treatment failure.

The third critical role of platelets is as amplifiers of inflammation in a process often termed thromboinflammation. Platelets interact with other innate immune cells, particularly neutrophils and monocytes, within the tumor microenvironment. This cross-talk creates a pro-inflammatory milieu that is highly conducive to tumor progression. This chronic, low-grade inflammation can lead to further DNA damage and genomic instability in cancer cells, promoting the selection of more aggressive and treatment-resistant clones.[13] It is this complex interplay of angiogenesis, metastasis promotion, and thromboinflammation that makes a high platelet count such a negative prognostic indicator. The platelets are not just markers; they are active drivers of the very processes that chemotherapy aims to halt. While the platelet count tells one half of the story, the other half is narrated by the denominator of the PLR: the absolute lymphocyte count. Lymphocytes, especially CD8+ cytotoxic T-lymphocytes, are the elite special forces of the adaptive immune system, engineered to recognize and eliminate malignant cells. A healthy peripheral lymphocyte count is the hallmark of a competent immune system capable of mounting a powerful anti-tumor response. The starkly inverse relationship observed in our study—where patients who responded best had the highest lymphocyte counts and those who progressed had the lowest—is a testament to the critical importance of this immune surveillance. The lymphocytopenia seen in patients with poor outcomes is not a random event; it is a sign that the host's defenses are crumbling under the weight of the malignant assault.[13]

There are multiple mechanisms by which a tumor can orchestrate the depletion and dysfunction of lymphocytes. Tumors are masters of immune evasion and can secrete a range of immunosuppressive cytokines, including TGF-β and IL-10, which directly inhibit T-cell proliferation and function.[14] They can also recruit and expand populations of regulatory immune cells, such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs), whose primary job is to actively shut down the activity of effector T-cells. Moreover, the chronic presence of tumor antigens can lead to a state of T-cell "exhaustion," a dysfunctional state where T-cells progressively lose their ability to secrete cytokines and kill target cells, eventually leading to their deletion through apoptosis.

The state of the immune system is also critically important for the efficacy of conventional chemotherapy. For a long time, chemotherapy was thought to work solely by directly killing rapidly dividing cancer cells. However, a more modern understanding reveals a crucial synergy with the immune system. Certain chemotherapeutic agents can induce a specific type of cell death known as immunogenic cell death (ICD).[15] When cancer cells die via ICD, they release a set of signals that act as an "eat me" signal to the immune system, attracting dendritic cells to the tumor site. These dendritic cells then process the tumor antigens and present them to T-cells, effectively vaccinating the host against their own tumor and priming a new wave of anti-tumor immunity to eliminate any residual disease. However, this entire synergistic process is contingent on the presence of a functional and sufficient pool of T-

lymphocytes. If a patient is lymphopenic at baseline, as was the case for our progressive disease group, their ability to capitalize on the immunogenic potential of chemotherapy is severely blunted. They lack the cellular machinery to mount an effective follow-up attack, allowing the cancer to regroup and progress. The low lymphocyte count is, therefore, a sign of a host that is ill-equipped to partner with therapy to achieve a durable response.

It is the brilliant synthesis of these two opposing biological narratives that gives the PLR its profound predictive power. A high PLR is the mathematical signature of a perfect storm for tumor progression: a system flooded with pro-tumorigenic, pro-angiogenic, and pro-metastatic platelets, while the army of anti-tumor lymphocytes is depleted and dysfunctional. It describes a biological landscape where the scales are heavily tipped in favor of the malignancy.[16] Conversely, a low PLR signifies a more favorable equilibrium: a less intense inflammatory drive and a more robust and competent immune system, creating a host environment that is more resistant to tumor growth and more receptive to the cytotoxic and immunogenic effects of chemotherapy.

The results of our statistical analysis provide a clear, quantitative validation of this biological model. The Kruskal-Wallis test confirmed that the differences between the groups were not due to chance. The subsequent Dunn's post-hoc tests provided the crucial evidence for a graded response, showing that each step down in treatment efficacy—from partial response to stable disease, and from stable disease to progressive disease—was accompanied by a statistically significant increase in the median PLR. This is a powerful finding, as it suggests a dose-response relationship between the degree of thromboinflammatory imbalance and the probability of treatment failure. The ROC curve analysis further solidified the clinical potential of this biomarker. An Area Under the Curve of 0.86 is considered good to excellent for a diagnostic or prognostic test, indicating that the PLR has a high degree of accuracy in distinguishing between patients who will and will not respond to treatment. The identification of a specific cut-off value of 185, with its associated high sensitivity and specificity, provides a tangible and testable threshold for future studies. In our cohort, this simple calculation provided a remarkably clear signal of a patient's likely therapeutic trajectory.[17]

The findings from our Palembang-based study were not generated in a vacuum. They resonate strongly with a vast and growing body of international literature that has consistently pointed to the prognostic significance of PLR and other inflammatory biomarkers in NSCLC and numerous other malignancies.[18] By confirming these associations with enhanced statistical rigor in a specific Southeast Asian population, our study adds a valuable piece to the global evidence map. It suggests that the fundamental biological principles linking systemic inflammation to cancer progression and treatment response are universally conserved across different ethnic and geographical settings. This consistency across studies strengthens the argument that the PLR is not just a statistical curiosity but a genuine and robust indicator of underlying cancer biology. It captures a fundamental truth about the disease: that the outcome of a patient's battle with cancer is determined not just by the characteristics of the tumor cells themselves, but by the complex, dynamic, and critically important dialogue between the tumor and the host's systemic environment.[19]

In essence, our detailed analysis provides a compelling narrative. It begins with the tumor's ability to corrupt the host's hematopoietic system, leading to an overproduction of platelets. These platelets then act as agents of chaos, promoting angiogenesis, shielding metastatic cells, and fanning the flames of inflammation. Simultaneously, the tumor wages a war of attrition against the immune system, depleting the ranks of the lymphocytes that are meant to protect the host.[20] The PLR, in its elegant simplicity, captures the net result of this internal conflict. The clear, graded, and highly significant results of our study demonstrate that by measuring this simple ratio, we can gain profound insight into which side is winning

this battle at the outset of therapy, and thereby predict, with a respectable degree of accuracy, the likely outcome of the treatment to come.

5. Conclusion

This comprehensive investigation into an Indonesian cohort with advanced-stage non-small cell lung cancer provides definitive and compelling evidence that the pre-treatment platelet-to-lymphocyte ratio is a powerful predictor of chemotherapy efficacy. The clear, graded increase in the PLR corresponding to a worsening clinical outcome is not merely a statistical observation but the clinical signature of a profound biological truth: the balance between the body's pro-tumorigenic inflammatory response and its anti-tumor immune defense is a critical determinant of a patient's therapeutic trajectory. A high PLR is the hallmark of a system where platelet-driven support for the tumor overwhelms a depleted lymphocytic defense, creating an internal environment that is inherently resistant to the effects of standard cytotoxic therapy. The robust predictive accuracy demonstrated by our analysis underscores the immense potential of this simple, inexpensive, and universally available biomarker. The PLR stands as a testament to the power of using readily accessible data to gain deep insights into complex disease biology, offering a tangible tool to help clinicians stratify risk, anticipate challenges, and move towards a more personalized and effective approach in the formidable fight against non-small cell lung cancer.

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