



## ANALYSIS OF THE RELATIONSHIP BETWEEN NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR), PLATELET-TO-LYMPHOCYTE RATIO (PLR), AND RED BLOOD CELL DISTRIBUTION WIDTH (RDW) WITH COLORECTAL CANCER STAGING

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### ABSTRACT

This study aimed to examine the relationship between the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) with colorectal cancer (CRC) staging. Colorectal cancer is one of the most prevalent malignancies worldwide and a leading cause of cancer-related mortality, particularly in Indonesia. Inflammation plays an important role in cancer progression, and systemic inflammatory markers such as NLR, PLR, and RDW are considered practical, accessible, and cost-effective indicators for assessing disease severity and prognosis. An observational analytic study with a cross-sectional design was conducted at H. Adam Malik General Hospital, Medan, from November 2024 to January 2025. A total of 56 newly diagnosed CRC patients who had not undergone surgery or chemotherapy were enrolled using consecutive sampling. Blood samples were analyzed using a Sysmex XN-1500 hematology analyzer. Statistical analyses included independent t tests, Mann–Whitney tests, Spearman correlation, and receiver operating characteristic (ROC) analysis. The results demonstrated a significant difference in PLR values between early- and advanced-stage CRC ( $p = 0.003$ ), with a moderate positive correlation between PLR and cancer stage ( $r = 0.297$ ,  $p = 0.026$ ). RDW showed a weak but statistically significant correlation with CRC stage ( $r = 0.284$ ,  $p = 0.034$ ). In contrast, NLR did not show a statistically significant correlation with CRC staging ( $p = 0.109$ ). These findings suggest that PLR and RDW are promising, simple, and inexpensive inflammatory biomarkers that may assist in the preoperative staging of colorectal cancer, whereas NLR alone may not be a reliable predictor of CRC stage.

Keywords: colorectal cancer; inflammation; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; red blood cell distribution width

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## INTRODUCTION

Colorectal cancer (CRC) is a malignancy arising from the colon or rectum and represents one of the most significant global cancer burdens. In 2020, CRC was the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide, accounting for approximately 1.9 million new cases and 0.9 million deaths (Xi & Xu, 2021). In Indonesia, CRC is among the top three causes of cancer-related mortality, with an incidence rate of 12.8 per 100,000 population and contributing to approximately 9.5% of all cancer-related deaths, as reported by GLOBOCAN (International Agency for Research on Cancer [IARC], 2020).

Tumor progression and dissemination in CRC are influenced by multiple clinicopathological factors, including tumor size, neurovascular and lymphatic invasion, resection margins, tumor location, molecular characteristics, and host inflammatory response (Hu et al., 2019; Barel et al., 2019). The tumor–node–metastasis (TNM) staging system remains the cornerstone for CRC

classification and guides therapeutic decision-making and prognostic evaluation (Park et al., 2016). Beyond tumor-related factors, inflammation has been recognized as a critical component in cancer development, promoting tumor growth, invasion, angiogenesis, metastasis, and unfavorable clinical outcomes (Coussens & Werb, 2002; Watson et al., 2019).

Systemic inflammation can be readily assessed using peripheral blood parameters, including leukocytes, neutrophils, lymphocytes, and platelets. Among these, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have emerged as reliable inflammatory biomarkers associated with prognosis in various malignancies, including colorectal cancer (Li et al., 2014; Lucas et al., 2017). Elevated NLR and PLR values have consistently been linked to poorer survival outcomes and more advanced disease stages (Cho et al., 2017; Zou et al., 2016). Neutrophils contribute to tumor progression by enhancing angiogenesis, facilitating tumor cell dissemination, and suppressing antitumor immune responses, thereby correlating strongly with adverse prognosis (Park et al., 2016; Coffelt, 2016). Platelets, on the other hand, play a pivotal role in inflammatory signaling and angiogenesis, and increased platelet counts may reflect more aggressive tumor behavior and invasive potential (Wellenstein et al., 2019; Sharma et al., 2014). Conversely, lymphocytes exert antitumor effects by inhibiting tumor growth and metastasis; thus, lymphopenia indicates impaired host immune surveillance against cancer (Solak Mekić et al., 2018; Liang et al., 2016).

The neutrophil-to-lymphocyte ratio (NLR) is calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count and has been widely investigated as an inflammatory and prognostic biomarker in colorectal cancer (Galdiero et al., 2013). Misiewicz (2023) reported an average area under the curve (AUC) value of 0.742 for NLR, with an optimal cutoff value of 3.31, yielding a sensitivity of 63.03% and a specificity of 62.55%. For the platelet-to-lymphocyte ratio (PLR), the reported average AUC was 0.648, with a cutoff value of 146.98, corresponding to a sensitivity of 67.83% and a specificity of 60.65% (Misiewicz, 2023).

Another hematological parameter, red blood cell distribution width (RDW), reflects variability in erythrocyte size and has emerged as a simple yet robust prognostic indicator in oncology. Elevated RDW levels have been consistently associated with poorer survival outcomes and adverse clinical characteristics, including advanced age, higher tumor stage, hypoalbuminemia, anemia, and the presence of comorbidities (Herraez et al., 2020; Väyrynen et al., 2018). Pedrazzani et al. (2020) identified an optimal RDW cutoff value of 14.1% for prognostic stratification in patients with colorectal cancer.

Collectively, NLR, PLR, and RDW represent inexpensive, readily available, and easily accessible systemic inflammatory markers that may aid in the early assessment and prognostic evaluation of colorectal cancer. Previous studies have demonstrated significant associations between these markers and local tumor invasion, lymph node involvement, and distant metastasis (Jia et al., 2015; Kim et al., 2017; Zou et al., 2016). Although various radiological modalities are currently employed for colorectal cancer staging, their high cost and limited accessibility in certain clinical settings underscore the need for alternative approaches. Therefore, the use of NLR, PLR, and RDW as inflammatory biomarkers may serve as a cost-effective adjunct for estimating colorectal cancer stage prior to definitive surgical intervention. Accordingly, this study aimed to evaluate the role of NLR, PLR, and RDW as inexpensive, easy-to-use, and patient-friendly preoperative predictors of colorectal cancer stage.

## **METHOD**

This observational analytical study employed a cross-sectional design to evaluate the relationship between the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) with colorectal cancer stage. The study was conducted at H.

Adam Malik General Hospital, Medan, Indonesia, from November 2024 to January 2025. Adult patients with newly diagnosed colorectal cancer who had not undergone surgical intervention, chemotherapy, or other medical treatments and who met the inclusion criteria were enrolled.

The minimum required sample size was 46 participants, and subjects were recruited using a consecutive sampling method. Peripheral blood samples were collected and analyzed using a Sysmex XN-1500 automated hematology analyzer (Sysmex Corporation, Kobe, Japan), which operates based on flow cytometry and electrical impedance principles. Laboratory procedures were performed according to standard operating protocols and included pre-analytical, analytical, and post-analytical phases. Quality assurance was maintained through daily internal quality control assessments.

Statistical analyses were performed using appropriate parametric and nonparametric methods. Independent t tests and one-way analysis of variance (ANOVA) were applied for normally distributed data, while Spearman's rank correlation coefficient was used to assess the association between inflammatory markers and colorectal cancer stage. Receiver operating characteristic (ROC) curve analysis was conducted to determine optimal cutoff values for NLR, PLR, and RDW. A two-tailed p value of < 0.05 was considered statistically significant.

## RESULT

Table 1.  
Demographic Characteristics of Research Subjects

Demographic Characteristics	n = 56
Sex, f (%)	
Man	31 (55,4)
Woman	25 (44,6)
Age year	
Rerata (SD)	55,71 (13,26)
Location, f (%)	
Colon	15 (26,8)
Rectal	23 (41,1)
Rectosigmoid	3 (5,4)
Saecum	3 (5,4)
Sigmoid	11 (19,6)
Kolonsigmoid	1 (1,8)
Metastasis, f (%)	
None	40 (71,4)
Liver	10 (17,9)
Lung	1 (1,8)
Liver and bone	1 (1,8)
Liver and lung	2 (3,6)
Uterus	1 (1,8)
Vulva	1 (1,8)
Stage, f (%)	
II	20 (35,7)
III	19 (33,9)
IV	17 (30,4)

The study subjects were predominantly male patients, totaling 31 individuals (54.9%). The average age of the patients was 55.71 years, with the youngest being 27 years old and the oldest 84 years old. The most common location of colorectal cancer was in the rectum, affecting 23 patients (41.1%). Metastasis was most frequently found in the liver, affecting 10 patients (17.9%). However, no metastasis was detected in 40 patients (71.4%). The most common stage in this study was stage II, affecting 20 patients (35.7%).

The mean hemoglobin level is 11.09 g/dL, with a minimum level of 4.6 g/dL and a maximum level of 15.3 g/dL. The mean platelet count is 364,410 thousand/ $\mu$ L, with a minimum level of 87

thousand/ $\mu$ L and a maximum level of 733 thousand/ $\mu$ L. The average absolute neutrophil count is 9.35 thousand/ $\mu$ L, with a minimum level of 0.99 thousand/ $\mu$ L and a maximum level of 40.52 thousand/ $\mu$ L. The average absolute lymphocyte count is 1.75 thousand/ $\mu$ L, with a minimum level of 0.55 thousand/ $\mu$ L and a maximum level of 3.82 thousand/ $\mu$ L. The average RDW is 16.25, with the lowest value of 11.7 and the highest value of 27.2. The average NLR value is 6.86, with the lowest NLR value of 0.45 and the highest value of 33.78. The PLR value is 252.68, with the lowest PLR value of 60 and the highest value of 868.35.

Table 2.

Characteristics of Colorectal Cancer Patient Laboratories

Variable	Mean (SD)
Hemoglobin, g/dl	11,09 (2,51)
Platelet, ribu/ $\mu$ L	364,41 (144,36)
Neutrofil Absolut, ribu/ $\mu$ L	9,35 (7,08)
Limfosit Absolut, ribu/ $\mu$ L	1,75 (0,84)
RDW	16,25 (3,58)
NLR	6,86 (6,68)
PLR	252,68 (154,87)

Table 3.

Differences in Laboratory Characteristics Based on Colorectal Cancer Stages

Variable	Advanced Stage n = 39	Early Stage n = 12	p
Hemoglobin, g/dL (SD)	10,94 (2,49)	11,36 (2,6)	0,560 <sup>a</sup>
Platelet, ribu/ $\mu$ L (SD)	371,78 (139,36)	351,15 (155,75)	0,613 <sup>a</sup>
Neutrofil Absolute, thousand/ $\mu$ L			
Median (Min – Max)	7,34 (2,11 – 20,35)	6,07 (0,99 – 40,52)	0,817 <sup>b</sup>
Limphosite Absolute, thousand/ $\mu$ L			
Median (Min – Max)	1,3 (0,55 – 3,37)	2,1 (0,79 – 3,82)	0,011 <sup>b</sup>
RDW			
Median (Min – Max)	16,55 (11,7 – 25,7)	14,5 (12,3 – 27,2)	0,090 <sup>b</sup>
NLR			
Median (Min – Max)	4,89 (1,73 – 33,78)	3,23 (0,45 – 29,3)	0,146 <sup>a</sup>
PLR			
Median (Min – Mak)	259,43 (116,3-731,94)	165,89 (60-868,35)	0,003 <sup>b</sup>

<sup>a</sup>T Independent, <sup>b</sup>Mann Whitney

The mean hemoglobin level in advanced colorectal cancer patients was 10.94 g/dL, while in early-stage patients it was 11.36 g/dL. Using an independent t-test, no significant difference in hemoglobin levels was found between advanced-stage colorectal cancer patients and early-stage colorectal cancer patients treated at H. Adam Malik General Hospital in Medan (p=0.560). The average platelet count in advanced-stage colorectal cancer patients was 371,78 thousand/ $\mu$ L, while in early-stage patients it was 351,15 thousand/ $\mu$ L. Using an independent t-test, no significant difference in platelet levels was found between the group of advanced colorectal cancer patients and the group of early-stage colorectal cancer patients treated at RSUP H. Adam Malik (p=0.613).

The median absolute neutrophil count in advanced-stage colorectal cancer patients was 7.34 thousand/ $\mu$ L, while in early-stage patients it was 6.07 thousand/ $\mu$ L. Using the Mann-Whitney U test, no significant difference in absolute neutrophil levels was found between the group of advanced-stage colorectal cancer patients and the group of early-stage colorectal cancer patients treated at RSUP Adam Malik Medan (p=0.817). The median absolute lymphocyte count in advanced-stage colorectal cancer patients was 1.3 thousand/ $\mu$ L, while in early-stage patients it was 2.1 thousand/ $\mu$ L. Using the Mann-Whitney test, a significant difference in absolute lymphocyte

counts was found between advanced-stage colorectal cancer patients and early-stage colorectal cancer patients treated at Adam Malik General Hospital in Medan ( $p=0.011$ ).

The median RDW in advanced colorectal cancer patients was 16.55, while in early-stage patients it was 14.5. Using the Mann-Whitney test, no significant difference in RDW was found between the group of advanced colorectal cancer patients and early-stage colorectal cancer patients treated at Adam Malik General Hospital in Medan ( $p=0.090$ ). The median NLR in advanced colorectal cancer patients was 4.89, while in early-stage patients it was 3.23. Using the Mann-Whitney test, no significant difference in NLR was found between the group of advanced colorectal cancer patients and early-stage colorectal cancer patients treated at Adam Malik General Hospital in Medan ( $p=0.146$ ). The median PLR in advanced colorectal cancer patients was 259.43, while in early-stage patients it was 165.89. Using the Mann-Whitney test, a significant difference in PLR was found between the group of advanced colorectal cancer patients and early-stage colorectal cancer patients treated at Adam Malik General Hospital in Medan ( $p=0.003$ ).

Table 4.

Correlation between RDW, NLR, and PLR and the stage of colorectal cancer

	stage of colorectal cancer	
	p*	R
RDW	0,034	0,284
NLR	0,109	0,216
PLR	0,026	0,297

\*Spearman

Using Spearman's correlation test, a significant correlation was found between RDW and colorectal cancer stage (0.034). The correlation value obtained was 0.284. The positive sign of the correlation value indicates that there is a direct correlation between RDW and colorectal cancer stage, meaning that an increase in RDW is followed by an increase in colorectal cancer stage. The level of correlation strength was weak ( $r > 0.2 - 0.4$ ). No significant correlation was found between NLR and colorectal cancer stage ( $p=0.109$ ). For the PLR parameter, there was a significant correlation with colorectal cancer stage ( $p=0.026$ ). The correlation value obtained was 0.284. A positive correlation value indicates that there is a direct correlation between PLR and colorectal cancer stage, meaning that an increase in PLR is associated with an increase in colorectal cancer stage. The strength of the correlation was found to be weak ( $r > 0.2 - 0.4$ ).

## DISCUSSION

This study found that the majority of patients with colorectal cancer (CRC) were male (55.4%). Data from the Global Cancer Observatory and population-based studies conducted in multiple regions of Indonesia indicate that both the prevalence and mortality of CRC are higher in men than in women (World Health Organization [WHO], 2020). This sex-related difference may be attributed, in part, to the protective effects of estrogen mediated through estrogen receptor beta ( $ER\beta$ ), which has been shown to function as a tumor suppressor in colorectal carcinogenesis among women (Caiazza et al., 2015). The mean age of patients in this study was 55.71 years. In Indonesia, the majority of CRC cases occur in individuals aged 50–54 years, and the risk of developing CRC increases substantially after the age of 50, accounting for more than 90% of cases (WHO, 2020; Vuik et al., 2019). Regarding tumor location, the rectum was identified as the most common site of colorectal cancer in this study (41.1%). Previous studies have similarly reported that colorectal tumors are most frequently located in the rectum and distal colon (Holtedahl et al., 2021). Lesions in the rectum are often detected earlier than those in other colorectal segments, largely due to their polypoid morphology and the relative ease of clinical and endoscopic examination (Baran et al., 2018).

In this study, the most frequently observed colorectal cancer (CRC) stage was stage II, accounting for 35.7% of cases. This finding is consistent with previous reports indicating that early-stage

disease (stages I–II) is commonly identified at diagnosis. Wang et al. (2019) similarly reported that stages I–II constituted the most prevalent stages, accounting for approximately 27% of cases. The absence of stage I CRC in the present study may be attributed to the tertiary referral nature of the hospital (type A hospital) and the nonspecific clinical manifestations of early-stage disease, which often delay diagnosis.

The mean hemoglobin (Hb) level in this study was 11.09 g/dL and did not differ significantly between early- and advanced-stage CRC ( $p = 0.560$ ). Although lower Hb levels have been associated with more advanced tumor stages in several studies (Väyrynen et al., 2018), other investigations, including that by Saidi et al. (2008), similarly found no significant association between hemoglobin levels and disease stage. These findings suggest that anemia in colorectal cancer is not solely attributable to tumor-related bleeding but may also result from systemic inflammatory responses and cytokine-mediated alterations in erythropoiesis.

The mean platelet count was higher in patients with advanced-stage disease ( $371.78 \times 10^3/\mu\text{L}$ ) compared with those in the early-stage group ( $351.15 \times 10^3/\mu\text{L}$ ); however, this difference was not statistically significant ( $p = .613$ ). Comparable results have been reported in previous studies, which demonstrated no significant association between platelet count and colorectal cancer stage (Al-Saeed et al., 2014; Wang et al., 2019). In contrast, other studies have identified thrombocytosis as a marker of advanced disease (Zhu et al., 2018). Variations in these findings may be influenced by confounding factors such as tumor burden, infection, systemic inflammation, or coexisting comorbidities (Zhou et al., 2017).

The mean absolute neutrophil count was higher in early-stage CRC ( $10.66 \times 10^3/\mu\text{L}$ ) compared with advanced-stage disease ( $8.63 \times 10^3/\mu\text{L}$ ), although this difference was not statistically significant ( $p = .817$ ). Zhou et al. (2017) suggested that neutrophil elevation represents an early inflammatory response to tumor development. The subsequent decrease observed in advanced stages may reflect increased recruitment of neutrophils into the tumor microenvironment, thereby reducing circulating neutrophil levels (Coffelt, 2016; Heshmat-Ghahdarjani et al., 2023). These findings support the notion that absolute neutrophil count alone is insufficient as a standalone marker for assessing cancer progression.

Furthermore, the median absolute lymphocyte count was higher in early-stage patients (2,100/ $\mu\text{L}$ ) compared with those in advanced stages (1,300/ $\mu\text{L}$ ), in line with the findings reported by Liang et al. (2016). Reduced lymphocyte counts have been associated with impaired antitumor immune responses, poorer prognosis, and decreased therapeutic efficacy, underscoring the importance of lymphocyte-mediated immunity in colorectal cancer progression.

The mean neutrophil-to-lymphocyte ratio (NLR) was slightly higher in patients with advanced-stage colorectal cancer (7.19) compared with those in the early stage (6.28); however, this difference was not statistically significant ( $p = 0.146$ ). In addition, no significant correlation was observed between NLR and cancer stage ( $p = 0.109$ ). Although several meta-analyses have reported an association between elevated NLR and advanced colorectal cancer stage (Jia et al., 2015; Li et al., 2014), other studies have failed to confirm this relationship. For example, Kwon et al. (2012) and Çakıt et al. (2023) found no significant association between NLR and tumor stage, suggesting that NLR alone may not be a reliable indicator of disease progression.

In contrast, the platelet-to-lymphocyte ratio (PLR) demonstrated more pronounced differences across disease stages. The mean PLR was significantly higher in advanced-stage patients (280.44) than in early-stage patients (202.71), and PLR showed a significant positive correlation with colorectal cancer stage ( $r = 0.284$ ,  $p = 0.026$ ). These findings are consistent with previous studies reporting that elevated PLR is associated with advanced disease stage and poorer prognosis in

colorectal cancer (Kim et al., 2017; Lu et al., 2017). A high PLR reflects platelet predominance relative to lymphocytes, indicating heightened systemic inflammation and a diminished antitumor immune response. Nevertheless, some studies have reported conflicting results, with no significant association observed between PLR and cancer stage (Turhan et al., 2021), highlighting the heterogeneity of findings across different populations. Red blood cell distribution width (RDW) did not show a statistically significant difference between early and advanced stages; however, a significant positive correlation with cancer stage was observed ( $r = 0.284$ ). This finding aligns with the results reported by Pedrazzani et al. (2020), who demonstrated that elevated RDW values were associated with more advanced colorectal cancer and poorer clinical outcomes. Increased RDW in advanced-stage disease is thought to reflect greater tumor burden and chronic systemic inflammation. Despite these observations, the prognostic role of RDW in colorectal cancer remains controversial due to variability in study designs, cutoff values, and patient populations.

## CONCLUSION

This study demonstrated that, among the evaluated hematological inflammatory markers, the platelet-to-lymphocyte ratio (PLR) and red blood cell distribution width (RDW) were significantly associated with colorectal cancer (CRC) stage, whereas the neutrophil-to-lymphocyte ratio (NLR) was not. The PLR showed a significant difference between early- and advanced-stage CRC and exhibited a positive correlation with tumor stage, indicating its potential value as a prognostic indicator. Similarly, RDW demonstrated a weak but statistically significant correlation with CRC stage, likely reflecting systemic inflammation and tumor burden. In contrast, although NLR values tended to be higher in patients with advanced-stage disease, no statistically significant difference or correlation with CRC stage was observed. These findings suggest that PLR and RDW may serve as simple, accessible, and cost-effective biomarkers to support the preoperative assessment of colorectal cancer, particularly in resource-limited settings. Nevertheless, further studies with larger sample sizes and longitudinal designs are warranted to validate these results and to better define their clinical utility in routine practice.

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